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## THE CELL THEORY ITS PAST, PRESENT AND FUTURE

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OF SCIENCE

AMONG the important meetings held by the American Association for the Advancement of Science at Richmond, Virginia, at the end of December, 1938, were those having to do with the cell theory—its development, present status and future possibilities. These meetings were in the nature of a symposium and combined the best thought of the three sections of the association (on history, botany and zoology) that collaborated in the program.

Seven outstanding papers by eminent scholars were presented in the two sessions, in the morning and afternoon of December 27. Those taking part were: Professor L. L. Woodruff, of Yale University; Professor J. S. Karling, of Columbia University; Professor E. G. Conklin, of Princeton University; Professor G. A. Baitsell, of Yale University; Professor Paul Weiss, of the University of Chicago; Professor Franz Schrader, of Columbia University; and Professor C. E. McClung, of the University of Pennsylvania. The present writer was called upon to organize the meetings on behalf of the three sections concerned and to carry out the easily fulfilled duties of editor.

The morning session, which was devoted to historical aspects, brought some surprising results, especially as bearing upon the two men, Schleiden and Schwann, who until the present day have generally been given most credit

with respect to the origin of the cell theory, which they were supposed to have enunciated about a century ago.

There is agreement in the papers presented by Professors Karling and Conklin that the cell theory was projected sometime prior to the appearance of the works of Schleiden and Schwann, that these two men added nothing either in content or in clarity with respect to the theory as such, and that they in fact lent support to a general view of cell formation which was completely erroneous.

Professor Woodruff deals with the preceding period and with the influence of the microscope. One hundred and seventy years before 1838 Robert Hooke had described little boxes or cells seen under the microscope, and from his day onward other significant observations on cells had been recorded by such men as Leeuwenhoek, Malpighi, Grew, Swammerdam and Wolff.

With the beginning of the nineteenth century, the cell theory came into sharper focus and received fairly clear and explicit delineation at the hands of Mirbel (1802 to 1809), Detrochet (1824), Turpin (1826), Meyen (1828 to 1838), Brown (1831), Demortier (1832), Purkinje (1835), Mohl (1835 to 1838) and Valentin (1838).

All these significant contributions preceded the works of Schleiden and Schwann. Why, then, it is asked, have these two men been called the founders of the cell theory? Why the amazing situation "that we still continue to call it after them"? It would seem, as suggested by Professors Karling and Conklin, that bluff and brag on Schleiden's part entered very largely into the picture. He underestimated, ignored or ridiculed really important contributions of predecessors and contemporaries and thus gained a wholly unwarranted recognition. And Schwann borrowed from Schleiden's arrogant claims as to plant cells and applied the same views to animal cells. As Professor Conklin concludes: "It would be more accurate as well as more becoming to strike out of our literature these personal possession tags attached to important discoveries, such as . . . 'the cell theory of Schleiden and Schwann.'"

The afternoon session of the symposium, devoted to the present and the future of the cell theory, developed what appears like a cleavage in points of view between those who see the problem primarily in terms of physical forces (of surface tensions, physical pressures and electrical attractions and repulsions) and those who hold that living matter exhibits certain characteristics (such as variability, selective direction and unfoldment in a temporal sequence) which sharply differentiate the organic from the inorganic.

It is generally agreed that the organization of the cell is exceedingly complex and that there is still much to be learned about it. Yet, on the one hand, as Professor Baitsell maintains, the difference between the organic and the inorganic is "not one of *kind* but merely of *degree of complexity*. . . . Since the same materials are used in both domains, they must conform to the same elemental patterns." Recent advances in cellular knowledge are in fact due primarily to the work of physicists and chemists. Professor Schrader, who is concerned chiefly with the present status of mitosis, sponsors the renewed consideration of a "dynamic" hypothesis. He suggests, however, that such a hypothesis meets with many difficulties, which recent findings have by no means mitigated, and that it is a foregone conclusion that the final explanation will not be as simple as had once been thought.

On the other hand, it is pointed out by Professor Weiss that, although "the cells derived from an egg have definite, innate capacities of their own . . . the fact that the individual cell can differentiate in a variety of directions but actually differentiates only in one, calls for factors which direct each cell selectively into its proper course. These factors, by their very nature, are super-cellular." They apparently derive from the organism as a whole and suggest the presence of what Professor McClung designates as "racial material in a linear order within the chromosomes. . . . Since living systems have unique phenomena of a higher order (than the non-living), like reproduction, metabolism and consciousness, it is only

logical to conclude that there must be units of a new order to explain them."

The participants in the afternoon meeting are in agreement that there is no sharp break between the living and the non-living. The progressive series of integrations does not stop at the molecular but continues to higher orders. Furthermore, the chemical elements found in the living orders and their physical and chemical properties and interactions are, it would seem, precisely the same as those found in the non-living orders. If there is difference of opinion it appears to be as to whether the integrations of a higher order (such as the cellular) can be completely explained in terms of principles derived from a lower order (such as the molecular) or whether, since the living order has properties not found in the non-living, it must have its own peculiar units and be explained primarily in terms of those units. The future, it is held, should soon bring us closer to a resolution of such disputed questions.

These most interesting and important papers are presented in the pages that follow, with very slight omissions here and there to avoid needless repetition.



## MICROSCOPY BEFORE THE NINETEENTH CENTURY

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Each adds a little to our knowledge of Nature, and from all the facts assembled arises grandeur.—*Aristotle.*

ON this centenary of the formulation of the cell theory, it appears meet and proper to take a passing glance at the pioneers in microscopy, because, in truth, "the succession of men during the course of many centuries should be considered as one and the same man who exists always and learns continuously." The real value of an individual's work can be appraised with accuracy only when it is projected against the background of the intellectual life of his time. Schleiden and Schwann were indeed heirs of the past as well as outstanding examples of the fact that "the man and the moment must agree" if far-reaching results are quickly to follow. The cell theory initiated a rejuvenation of nearly all the chief branches of biological science, until to-day, as Lillie has recently emphasized, the cell has become "a sort of half-way house through which biological problems must pass, going or coming, before they complete their destiny."

The macroscopical anatomical techniques were the sole resort of naturalists until magnification was put into their hands to become the outstanding technique that actually created biological science—reduced the botanical and the zoological fields to a common denominator, the cell. As Sachs (1890) has, in effect, said,

the use of magnifying glasses taught those who used them to see scientifically and exactly. In arming the eye with these increased powers the attention was concentrated on definite points in the object, and observation had to be accompanied by conscious and intense reflection, in order to make the object, which is observed in part only by the microscope, clear to the mental eye in all the relations of the parts to one another and to the whole. Therefore, in marked contrast with the extremely slow progress in obtaining a mental mastery over the macroscopic morphological features of plants and animals is the work of the early students with the microscope.

Although the science of optics formally starts with Euclid, apparently what may be regarded as the earliest observations involving magnification are those of Seneca, who, during the first century of the Christian era, noted that small letters appear relatively large and clear when viewed through a glass globe filled with water; a result he attributed to the nature of the medium rather than to the curvature of the surface. Moreover, it appears that several Arabian opticians and other medieval savants were familiar with some of the properties of curved reflecting surfaces afforded by hemispheres and spheres of glass, but there seems to be no evidence that the possibilities of a lens as an optical instrument were appreciated until near the close of the thirteenth century. Roger Bacon indeed says: "If one views letters or any minute object through a lesser segment of a sphere of crystal or glass or other transparent substance, whose plane base is laid upon them, they will appear much larger and better. . . . Such an instrument is useful to old persons and to those with weak eyes." However, Bacon made no significant advance in the theory or the use of lenses, though possibly it is true, as suggested by Singer, "that groping with the instinct of genius, he did vaguely foresee both telescope and compound microscope."

The actual invention of convex spectacles probably did not occur until shortly after Bacon's death, and flourished when polishing lenses by a revolving lap was superseded by grinding with a spherical tool having the same curvature as that of the desired lens. The value of spectacles, apparently first appreciated by the illuminators of manuscripts, gradually filtered through to the populace, while the optical properties of lenses were studied by many, including Leonardo da Vinci, Leonard Digges, and Francesco Maurolico who reputedly was the first to use the theory of glass lenses to explain the operation of the lens of the eye. Moreover, Gianbattista della Porta stated in 1589 that "if you know how to combine the two kinds (con-

vex and concave lenses) properly you will see both things afar off and things neer hand, both greater and clearer"—one of several contemporary suggestions of some sort of bilenticular system.

Although the enthusiasm for optics at this period was largely motivated by a desire to improve spectacle lenses, concurrently occurred the first feeble impact of lenses upon biology if one may judge by the account of the itch-mite by Thomas Mouffet in 1589 (published posthumously in 1634) and by figures of magnified organisms from the hands of George Hoefnagel in 1592 and Fabio Colonna in 1606. But even this was premature because the actual stimulation of investigation necessarily awaited more efficient lenses of very short focus and high magnifying power, as well as the effective discovery that two lenses can be adjusted in a system with still greater potentialities. The latter was accomplished during the fading years of the sixteenth century, apparently first by Dutch spectacle-makers, Hans and Zacharias Jansen, who placed, perhaps accidentally, two convex lenses in proper relative positions in a tube so that they acted as a true compound microscope, the image formed by the objective being magnified by the ocular before reaching the eye. Before long the invention came to the attention of Galileo who thereupon, in 1609, says he discovered the principle involved by a process of reasoning. However, the Galilean instrument gave no intermediate image and so was not a compound microscope according to the usual modern definition—a "true" compound microscope not reaching Galileo until 1624, and then indirectly from the Jansens.

At all events, the significant fact is that to Italian skies belongs the honor of reaping the first fruits of the use of a bilenticular system. Galileo in 1610 effectively employed the instrument and made the first recorded observations which during the following two decades encouraged microscopical studies by his associates in that brilliant coterie of scholars, led by Federigo Cesi, Duke of Aqua-

sparta, who met under the title of the Accademia dei Lincei. Prominent among the members were the botanist Colonna, the naturalist and scholar Stelluti, the astronomer Fontana, the Papal physician Faber and, until his death in 1615, the versatile sage and optician, Porta. Unfortunately few of their observations have reached posterity, other than those of Cesi on the "seeds" of ferns that entitle him to be regarded as the discoverer of spores, and those of Francesco Stelluti on bees, with the first published figures made with a compound microscope. (Fig. 1.)

Simple lenses were, of course, in more general use. It will be recalled that William Harvey in his classic of 1628 noted that he had seen with his *perspicillum* the beating heart of wasps, hornets and flies. So it was from these small beginnings with lenses, singly and in combination, that the urge for magnification in the biological field crept over western Europe, until toward the middle of the seventeenth century many were turning their hands to improving the compound microscope and their eyes to sporadic observing.

Probably the most significant gleanings of this period are in the works of the Sicilian Gianbattista Hodierna and the Neapolitan Francisco Fontana. The former published, in 1644, an investigation on the eyes of about thirty species of insects, and the latter, in 1656, miscellaneous observations including some on mites and several insects. And at the same time the encyclopedic Athanasius Kircher exploited the use of the microscope. He says, "Numbers of things might be discovered . . . facts hitherto unknown by all medical men and investigated by none of them," but he himself gave no detailed descriptions or figures of anything that magnification had revealed to him. However, during the next decade the gifted physician of Paris, Pierre Borel, was using the microscope to study a wide variety of objects and perhaps had a glimpse of human red blood cells. In 1656 he published the first volume devoted solely to microscopy. Ac-

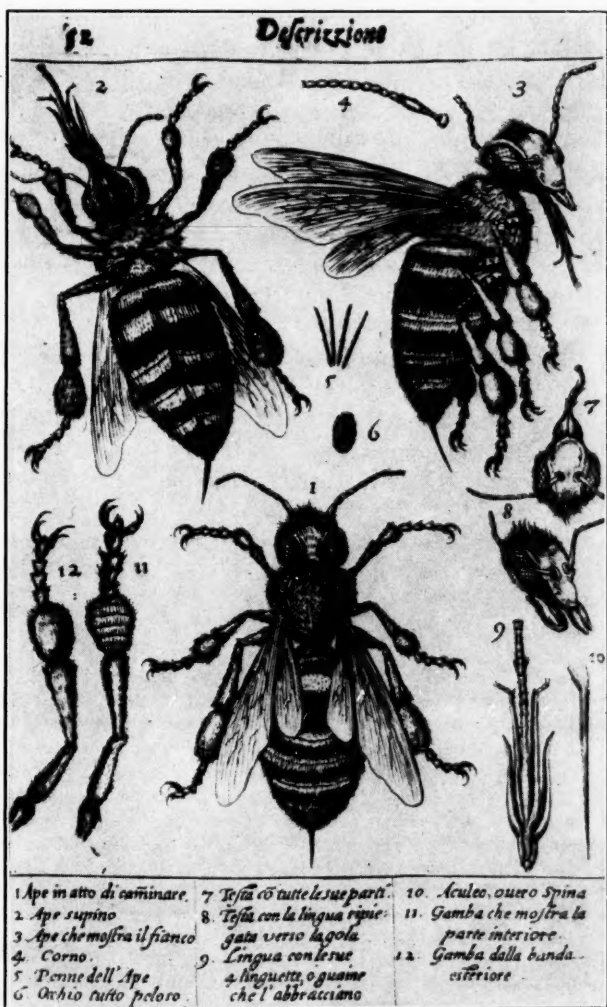


FIG. 1. Figures of Bees by Francesco Stelluti, first published in 1625. From "Descrizione dell' Ape," in Stelluti's "Persio Tradotto," Rome, 1630.

According to Singer, he records minute markings on young leaves which probably were outlines of cells, and not only saw stomata but also realized their power of opening and closing. And he describes what perhaps was protoplasmic movement. Moreover, apparently he was the first not only to turn the microscope on the early stages of the developing chick, but also to put the instrument to practical use in his profession—he was able to see ingrowing eyelashes and relieve a patient—the first use of the microscope in the field of medicine. (Singer, 1914, 1915; Torrey, 1938.)

But it appears that an Englishman, Robert Hooke, was the first to realize to the full the importance of studying nature with instruments which increase the powers of the senses in general and of vision in particular, and to convincingly express it in a most remarkable book published with the imprint of the Royal Society of London in 1665. Hooke (1665a) called his treatise "*The Micrographia; or Some Physiological Descriptions of Minute Bodies Made by Magnifying Glasses and Enquiries Thereupon*," and emphasized the need to supply the

infirmities (of the senses) with Instruments, and, as it were, the adding of artificial Organs to the natural. . . . One of them has been of late years accomplished with prodigious benefit to all sorts of useful knowledge, by the invention of Optical Glasses. . . . By the help of Microscopes, there is nothing so small, as to escape our inquiry. . . . By this the Earth it self . . . shews quite a new thing to us, and in every little particle of its matter, we now behold almost as great a variety of Creatures, as we were able before to reckon up in the whole Universe it self. It seems not improbable, but by these helps the subtilty of the composition of bodies, the structure of their parts, the various texture of their matter, the instruments and manner of their inward motions, and all the other possible appearances of things, may come to be more fully discovered. . . .

This is not the place to evaluate the many contributions to science made by the author of the "*Micrographia*" nor indeed by the book itself because, as a contemporary reviewer remarked, "This book contains more than can be taken notice of in an extract." But one observation, in particular, holds our attention. This is "Observ. XVIII.



Of the Schematisme or Texture of Cork, and of the Cells and Pores of some other such frothy Bodies." Here are described and emphasized for the first time the "little boxes or cells" of organic structure and the use of the word "cell" is, of course, responsible for its application to the protoplasmic units of modern biology. And as if Hooke sensed the importance of this observation, he selected it to illustrate his method of scientific inquiry in a later treatise. (Fig. 2.)

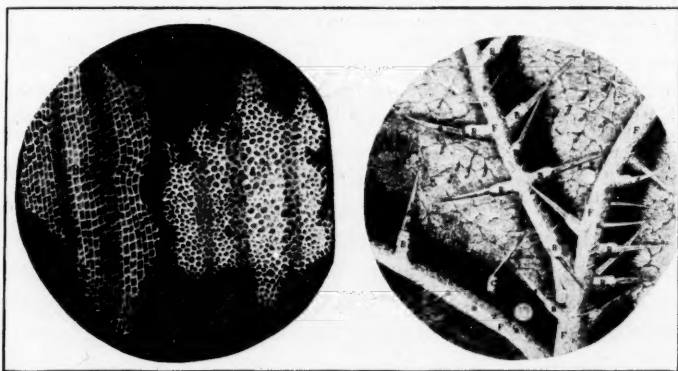


FIG. 2. Section of Cork, and Surface of Nettle Leaf. Hooke's "Micrographia," 1665.

The historic significance of Hooke's observations on cork (1665b) demands that he speak briefly for himself:

I took a good clear piece of Cork, and with a Pen-knife sharpen'd as keen as a razor, I cut a piece of it off, and thereby left the surface of it exceeding smooth, then examining it very diligently with a *Microscope*, me thought I could perceive it to appear a little porous; but I could not so plainly distinguish them, as to be sure that they were pores, much less what Figure they were of: But judging from the lightness and yielding quality of the Cork, that certainly the texture could not be so curious, but that possibly, if I could use some further diligence, I might find it to be discernable with a *Microscope*, I with the same sharp pen-knife, cut off from the former smooth surface an exceeding thin piece of it, and placing it on a black object Plate, because it was it self a white body, and casting the light on it with a deep *plano-convex* Glass, I could exceedingly plainly perceive it to be all perforated and porous, much like a Honey-comb, but that the pores of it were not regular; yet it was not unlike a Honey-comb in these particulars.



First, in that it had a very little solid substance, in comparison of the empty cavity that was contain'd between. . . .

Next, in that these pores, or cells, were not very deep, but consisted of a great many little Boxes, separated out of one continued long pore, by certain *Diaphragms*. . . .

I no sooner discern'd these (which were indeed the first *microscopical* pores I ever saw, and perhaps, that were ever seen, for I had not met with any Writer or Person, that had made any mention of them before this) but me thought I had with the discovery of them, presently hinted to me the true and intelligible reason of all the *Phaenomena* of Cork. . . .

For . . . our *Microscope* informs us that the substance of Cork is altogether fill'd with Air, and that that Air is perfectly enclosed in little Boxes or Cells distinct from one another. . . .

Nor is this kind of Texture peculiar to Cork onely; for upon examination with my *Microscope*, I have found that the pith of an Elder, or almost any other Tree, the inner pulp or pith of the Cany hollow stalks of several other Vegetables: as of Fennel, Carrets, Daucus, Bur-docks, Teasels, Fearn, some kinds of Reeds, &c. have much such a kind of *Schematisme*, as I have lately shewn that of Cork. . . .

And then Hooke made significant observations which showed that some cells are not filled with air. He saw the sap and probably actually had a glimpse of protoplasm. He says; ". . . in several of those Vegetables, whil'st green, I have with my *Microscope*, plainly enough discover'd these Cells or Pores fill'd with juices, and by degrees sweating them out: as I have also observed in green Wood all those long *Microscopical* pores which appear in Charcoal perfectly empty of any thing but Air."

Again, a later study, "Of the stinging points and juice of Nettles, and some other venomous Plants" (Hooke, 1665c; Woodruff, 1919), is accompanied by a figure of the lower side of a nettle leaf in which the outlines of the epidermal cells are well delineated. And Miall (1912) remarks that "there is something very like a nucleus in one of them, but this may be accidental." However, Hooke did not emphasize any relationship between the structures he observed in the nettle and in cork.

With these few quotations we must leave the "Micrographia"—the first detailed and precise microscopical observations extant—with the thought that it had an immense influence, gleanings from its wealth of beautiful

plates "embellishing" technical and popular manuals on the microscope for a century and a half. While the book was being written, Samuel Pepys purchased a microscope and thought five pounds, ten shillings "a great price for a curious bauble." And it is not recorded that Hooke's demonstrations or those of the contemporary London physician, Henry Power (1664), changed his opinion, but the fact remains that from this time on magnification was established as a fundamental and indispensable aid in biological research. The so-called classical period in microscopy unfolds during the latter part of the seventeenth century with the outstanding contributions of Leeuwenhoek, Malpighi, Grew and Swammerdam. They literally created a new world and reversed the former conception that interest in objects is proportionate to their size.

The recluse of Delft, Antony van Leeuwenhoek, spent a long life in placid observations with simple microscopes made by his own hands. But his observations were exciting, for his lenses revealed a hitherto unseen world of living things—some so small that, as he says, "ten thousand of these living creatures could scarce equal the bulk of a coarse sand-grain." His acumen and patience produced the longest and most important series of communications that a scientific society has ever received, extending over a period of more than fifty years. The last letter was addressed to the Royal Society of London from his death-bed in his ninety-first year.

Leeuwenhoek's discovery of the Protozoa is described in a letter written in 1674. He says that in examining some pond water he observed "very many little animalcules, whereof some were roundish. . . . Others were somewhat longer than an oval, and these were very slow a-moving, and few in number. . . . And the motion of most of these animalcules in the water was so swift, and so various, upwards, downwards, and round about, that 'twas wonderful to see. . . ."

Such was his—and the world's—first glimpse of animal-

cules, but the most famous "letter on the Protozoa" was penned in 1676. Thanks to a remarkably thorough study of Leeuwenhoek and his work recently made by Dobell (1932), we now have available for the first time not only the complete contents of this letter, but also a revised translation of the part originally published. The classic account of the discovery of *Vorticella* is still more informative in its new dress—the first description of an identifiable Protozoon.

So Leeuwenhoek put the Protozoa within the view of science, and then further on in this letter he did the same for Bacteria. In describing his first observations on pepper-water, he says: "The fourth sort of little animals, which drifted among the three sorts aforesaid, were incredibly small; nay, so small, in my sight, that I judged that even if 100 of these very wee animals lay stretched out one against another, they could not reach to the length of a grain of coarse sand. . . ."

Leeuwenhoek's observations were by no means confined to the world of "animalcules." He turned his lenses to the spinning glands of spiders, pupae of ants, eggs of aphids, embryos of mussels, blood corpuscles and capillaries, the structure of muscle, transverse and longitudinal sections of many kinds of wood, and so on (Leeuwenhoek, 1722; Hoole, 1800-1807). And even to-day one marvels that Leeuwenhoek could see so much with his simple lenses. Although he was generous with his microscopes, his "particular method of observing" was persistently kept for himself alone. Dobell believes that Leeuwenhoek used some method of dark-ground illumination and this, in part at least, is almost surely the solution of his secret. (Fig. 3.)

Although Leeuwenhoek complained: "I oftentimes hear it said that I do but tell fairy-tales about the little animals," confirmation gradually came from Hooke, Bonanni, King, Harris, Gray and an anonymous contributor to the *Philosophical Transactions*, as well as from Christiaan Huy-

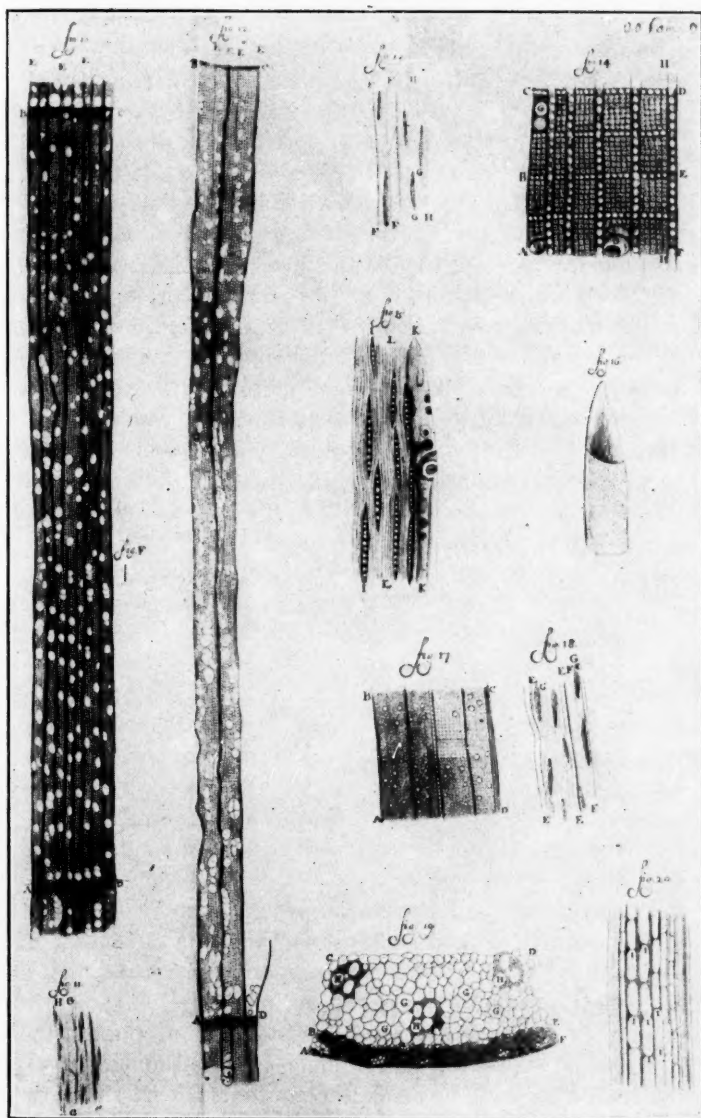


FIG. 3. Plant Tissues. Leeuwenhoek's "Anatomia seu Interiora Rerum, etc., 1687.

gens, though the important observations of the latter, transmitted to Leeuwenhoek in 1678, were not in print until recently (Hooke, 1678; Bonanni, 1691; King, 1693; Harris, 1696; Gray, 1696; Anon., 1703; Huygens, 1899). Then in 1718 appeared the first special treatise on animalcules in general and the Protozoa in particular by Louis Joblot of Paris. This is a remarkable book that describes new microscopes and many new organisms, and makes the first general attempt to give the latter appropriate names. Furthermore, in the study of the origin of the organisms Joblot was the first to boil infusions in order to eliminate life; a method-exploited in studies on biogenesis by Spallanzani and others over a half century later without a thought of Joblot. It was Dr. John Hill, who, in 1752, gave the first formal classification of animalcules and, as he says, "arranged them into a regular method, and gave them denominations"—one, the familiar *Paramecium*. Then Linnaeus in the twelfth edition of his "*Systema Naturae*" grouped all of them under three genera. And finally O. F. Müller (1773, 1786) closed the century for animalcules by publishing the first extensive taxonomic monographs on these forms.

While these and other studies on microscopic organisms were enlivening every drop of water, concomitant progress was, of course, being made in revealing some of the main outlines of the finer structure of higher plants and animals under the initial stimulus of Leeuwenhoek and his contemporaries—Malpighi in Italy, Grew in England and Swammerdam in Holland.

Marcello Malpighi spent most of his life as professor of medicine at Bologna and almost continuously devoted himself to a varied program of investigations with the microscope. His versatility as well as his genius is shown in particular by his studies on the anatomy of plants, the function of leaves, the development of the plant embryo, the embryology of the chick, the anatomy of the silkworm and the structure of glands. Skilled in microscopic anat-

omy but with prime interest in the physiological aspects of organisms, his most significant contribution lies in his dependence upon the microscope for the solution of problems where structure and function, so to speak, merge, which is well illustrated by his ocular demonstration of the capillary circulation in the lungs. This was published in 1661, before Leeuwenhoek's similar studies, and is the initial discovery of prime importance made with the microscope because it completed Harvey's work on the circulation of the blood. Malpighi wrote: "I saw with mine eyes a truly great thing. . . . It is clear to the senses that the blood flowed away along tortuous vessels and was not poured into spaces, but was always contained within tubules, and that its dispersion is due to the multiple winding of the vessels." (Fig. 4.)

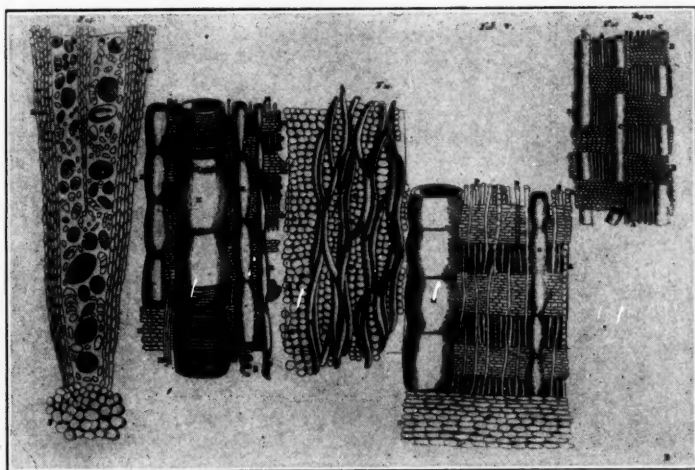


FIG. 4. Plant Tissues. Malpighi's "Anatome Plantarum," 1675-79.

Moving from Italy to England, we come upon the London physician, Nehemiah Grew (1672, 1682), who devoted most of his life to an intensive study of plant anatomy, and in this one field he paralleled, and perhaps surpassed, his Italian contemporary. Grew's work culminated in the



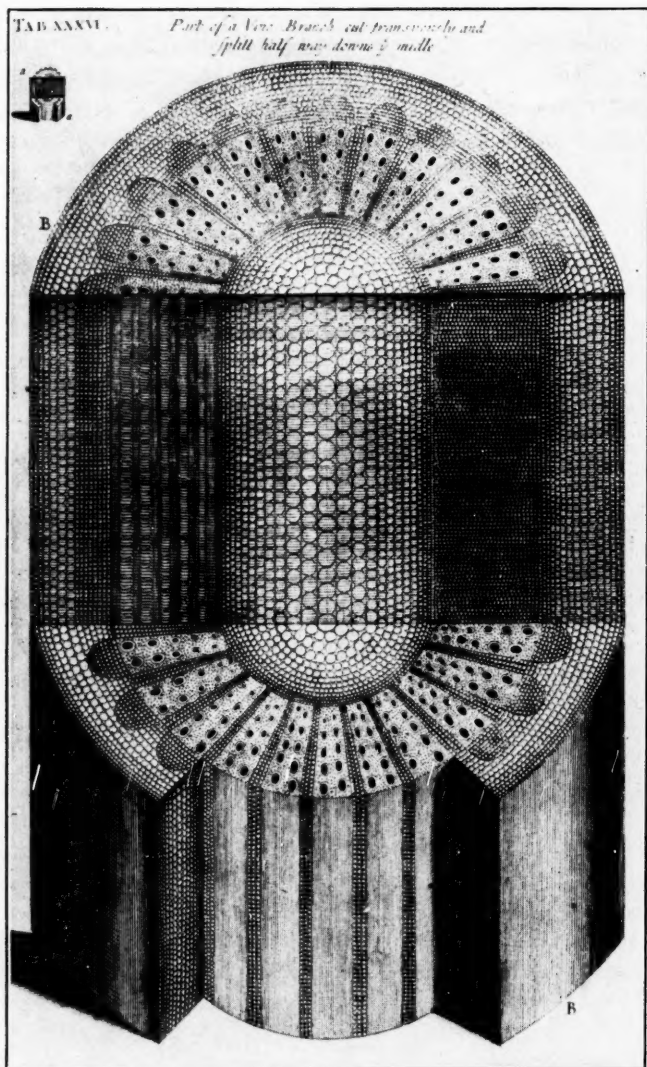


FIG. 5. Vine Branch. Grew's "Anatomy of Plants," 1682.



publication of his great "Anatomy of Plants" in 1682, several years after Malpighi's "Anatome Plantarum." The similarity of many of the observations unfortunately raised the question of Grew's indebtedness to Malpighi, but the implied slur is without the least foundation in fact. It was merely a case of two great pioneers working on essentially the same material at about the same time. Indeed, Grew voluntarily abandoned any claim to priority in regard to the discovery of vessels in plant stems and Malpighi undertook a Latin translation of Grew's work. (Fig. 5.)

Quite a different-tempered man was Jan Swammerdam, then at work in Holland on a magnificent series of animal dissections. By intensive application to exacting observations he ruined his health, but during his short lifetime he amassed sufficient material to support his chief thesis that the lower animals are as complexly constructed as the higher. Most of his observations were not published until over sixty years after his death, when they were collected in two splendid folios, profusely illustrated, under the title "*Biblia Naturae*" (Swammerdam, 1737-38; Hill, 1758). Some of the figures have never been excelled, and their range is wide, including, among others, the May fly, dragon fly, bee, ant, grasshopper, gall-insect, butterfly, hermit crab and tadpole. Swammerdam attained the last details visible with his single lenses, aided by a remarkable delicacy of manipulation of scalpel, forceps and injection technique. The work has been described, and probably justly, as the finest collection of microscopical observations ever produced by an investigator in this field. (Fig. 6.)

Strange to say, these pioneers with lenses, in particular Leeuwenhoek, Malpighi, Grew and Swammerdam, who created the golden age of microscopy, produced little immediate stimulation. This probably was in part due to the philosophically disturbing complexity of living things that overawed the naturalist, and to the fact that the pioneers collectively saw nearly all that was possible with the

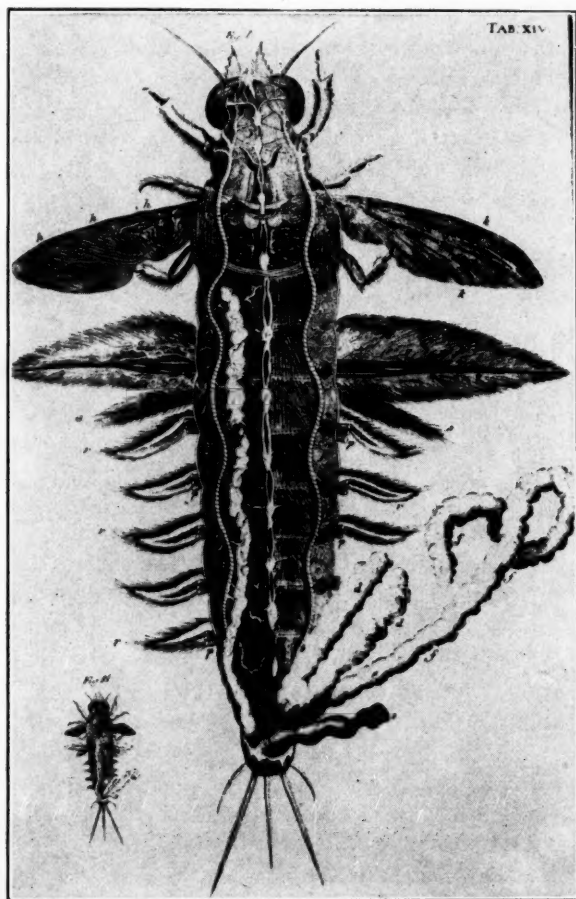


FIG. 6. May Fly, 1675, from Swammerdam's "Biblia Naturae," 1737-38.

available technique. The seeming finality of some of the work, such as that on the anatomy of plants, suggested the sterile notion that the subject was essentially exhausted. Indeed, it *was* exhausted for men of lesser capabilities. In general, what had been contributed to the stream of ideas that was destined a century and a half later to broaden out as the cell theory?

Malpighi, Grew and Leeuwenhoek were quite familiar with the elements that Hooke called cells. Malpighi referred to them as utricles, globules and saccules, and observed that their walls could be separated and the utricles isolated, so naturally he thought of the plant body in general as representing a union and coalescence of innumerable similar elements. Grew regarded the fundament of plant tissues as a fibrous "parenchymous" material with the fibers usually "woven and wound up" into an "infinite number of little cells or bladders" so that the whole is not unlike the "froth of beer" or a "piece of fine manchet." Vessels are formed by the confluence of "one single row or file of bladders evenly and perpendicularly piled." Leeuwenhoek described globules in the tissues of plants and animals. Thus he noted that leaves, with the exception of their vessels and fibers, are composed of globules which form not only a membrane on the surface but are variously placed and aggregated, and he discussed the nutritive supply of the globules with reference to the vessels. And Swammerdam, who was intent on organs rather than tissues, now and again mentions globules when using his higher lenses.

Naturally, as well as necessarily, the pioneers were more interested in what is now called histology than in cytology. They attempted to envisage the whole from the data at hand—and prematurely because, as it now appears, a sufficiently deep level of analysis had not been reached to render synthesis profitable. Thus Grew (1682a) in his "Anatomy of Plants" wrote:

The most unfeigned and proper resemblance we can at present make of the whole *Body* of a *Plant*, is to a piece of *fine Bone-Lace*, when the *Women* are working it upon the *Cushion*; for the *Pith*, *Insertions* and *Parenchyma* of the *Barque*, are all extream *Fine* and *Perfect Lace-Work*; the *Fibres* of the *Pith* running *Horizontally*, as do the *Threads* in a Piece of *Lace*; and bounding the several *Bladders* of the *Pith* and *Barque*; as the *Threds* do the several *Holes* of the *Lace*; and making up the *Insertions* without *Bladders*, or with very small ones, as the same *Threds* likewise do the *close Parts* of the *Lace*, which they call the *Cloth-Work*. And lastly, both the *Lignous* and *Aer-Vessels*, stand all *Perpendicular*, and so cross to the *Horizontal Fibres* of all the said *Parenchymous Parts*; even as in a piece of *Lace* upon the *Cushion*, the

*Pins* do to the *Threds*. The *Pins* being also conceived to be *Tubular*, and prolonged to any length; and the same *Lace-Work* to be wrought many Thousands of times over and over again, to any thickness or hight, according to the hight of any *Plant*. And this is the true *Texture* of a *Plant*; and the *general composure*, not only of a *Branch*, but of all other *Parts* from the *Seed* to the *Seed*.

And so the problem stood in general unchanged for upward of a hundred years. True, the eighteenth century produced a considerable number of students who turned their lenses on plant and animal structure, but none made impellingly significant observations except Caspar Friedrich Wolff (1759, 1768). Unlike his predecessors, he approached problems of the structure and development of organisms at a time when biologists were plagued by the doctrine of preformation, or "evolution" in the terminology of the period, and he planned his work to establish an inductive foundation for epigenesis in individual development. His famous doctoral dissertation, "Theoria Generationis," published in 1759 when he was twenty-six years of age, was the most important contribution since those of the classical microscopists, though it, as well as his later work, was almost completely disregarded by zoologists and botanists for some forty years. Its philosophical bearing was out of tune with those of the times, as represented, for example, by the ideas of Haller, the "abyss of learning" of the period. (Fig. 7.)

At the moment our interest in Wolff is not his insistence on epigenesis until it reached a *reductio ad absurdum* and tried to get something out of nothing, but the fact that he studied both plants and animals in a consistent effort to resolve their finer structure to a common denominator—to follow the process of development from the initial formation of tissue. Thus the embryonic parts first appear, he believed, as a transparent, gelatinous material which becomes saturated with a nutrient fluid. This sap is secreted in tiny droplets forming vesicles which gradually increase in size until as *Bläschen* or *Zellen* they become contiguous, except for the remnants of the substance be-

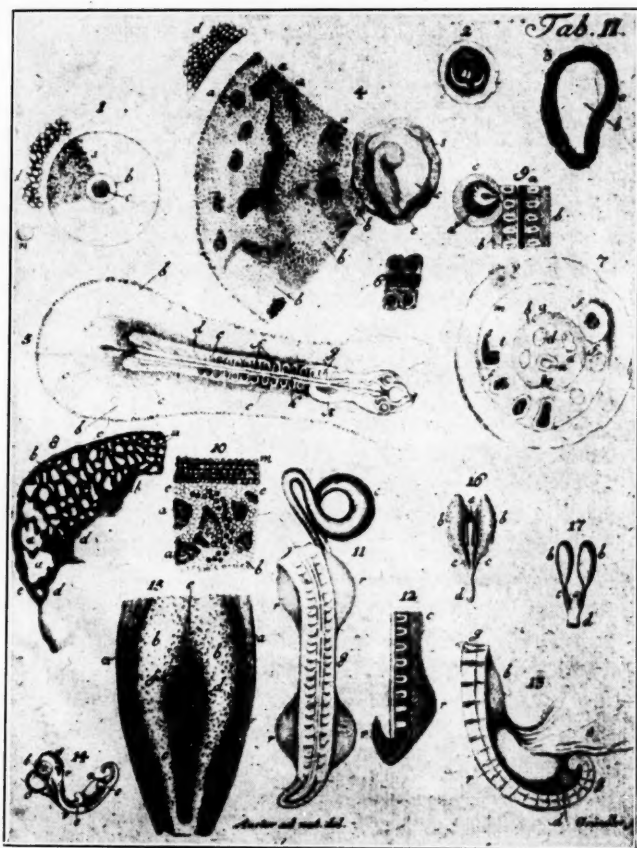


FIG. 7. Plate from Wolff's "Theoria Generationis," 1759.

tween, and so form what to-day we recognize as cells and cell walls. In general one is reminded of Grew's beer froth. Obviously, according to this scheme of cell formation the entities would be separated by a single lamina in a common matrix, though he believed there was communication between the cell cavities. And growth, he thought, takes place by the enlargement of existing cells as well as by the interpolation of new ones between the old. In brief,

the tissues of plants arise from one and the same fundamen-  
ment, variously modified.

Identical in principle according to Wolff is the under-  
lying process of development in animals. He says that  
"the particles which constitute all animal organs in their  
earliest inception are little globules, which may always be  
distinguished under a microscope with moderate magnifi-  
cation." The formation of the intestine of the chick, for  
example, is from a relatively homogeneous substance by  
gradual differentiation, as in the case of the meristem in  
plants, and therefore the processes of nutrition and growth  
are essentially the same in both animals and plants.  
Doubtless influenced by his study of growing points in  
plants, he compared the genesis of animal organs to leaves  
or layers—the ancestor of the "germ layers" of a later  
day. Wolff undeniably laid the foundation for a broad  
understanding of the essential similarity of the formative  
elements of plants and animals, but this was not to be built  
upon until after the turn of the century.

Perhaps the most interesting contributions in the in-  
terim were Hill's "Construction of Timber," published  
in 1770, and Hedwig's "*De Fibrae Vegetabilis et Animalis  
Ortu*," dated 1789. Hill's sections of wood are not very  
highly magnified, but his figures and descriptions are in  
some cases quite good. That he approached as near as, but  
no nearer than his predecessors to a true concept of the  
basic structure is evident, for example, from his remark  
that in section "the corona is a ring usually more or less  
angulated in its outline, placed between the pith and the  
wood in all vegetables. The general circle is cellular,  
composed of blebs and vessels, as the bark and rind, and  
is perfectly of their nature; only that at different distances  
are disposed among it oblong clusters of different vessels."  
And in describing the pith of the rose, he says, "It has,  
in a slice of this thickness, the appearance of starry forms,  
with oval rays; but this illusion vanishes on cutting a  
thinner piece. When one is viewed of a thousandth part  
of an inch they appear only simple blebs." (Fig. 8.)

# CONSTRUCTION O F T I M B E R,

From its EARLY GROWTH;

Explained by, the

## M I C R O S C O P E,

And proved from

## E X P E R I M E N T S,

### In a great VARIETY of KINDS:

### I N F I V E B O O K S.

On the PARTS of TREES; their VESSELS; and their  
ENCREASE by GROWTH: And on the different  
DISPOSITION of those PARTS in various KINDS;  
and the PARTICULARITIES in their VESSELS.

WITH FIGURES OF

Their various APPEARANCES; of the INSTRUMENT for  
cutting them; and of the MICROSCOPE thro' which  
they were viewed.

---

By JOHN HILL, M.D.

MEMBER of the IMPERIAL ACADEMY.

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M.DCC.LXX.

FIG. 8.

Hedwig's contribution, according to the interpretation of Sachs, shows careful observation though tinged with certain preconceived notions. His figures seem to be better than those of any of his predecessors. He saw cells aplenty, such as the epidermal cells of leaves, various parenchymatous tissues, and so on, but he regarded them all as vessels in the current indefinite sense of that term. And the record of the century should not be closed without mentioning Prochaska's "De Structura Nervorum," published in 1779, and Fontana's "De Venin de la Vipere,"



in 1781, both of which emphasized globules as important formative elements of the various tissues studied. But it is fair to say that these and other contributions, some of them "highly unimportant," gave no prophecy of the significance to be attained by cells during the dawning century.

Before leaving the development of this picture to others in this Symposium, we must consider the history of the microscope and microscopical technique which were silent but no less indispensable contributors to the formulation of the cell theory. "The history of the sciences," as Lillie (1938) remarks, "may be presented primarily as a history of ideas, but there would be no richness of ideas in science as we actually possess without richness in technique." Sometimes, to be sure, technique outruns ideas, and temporary sterility follows, but usually both surge ahead together. (Fig. 9.)

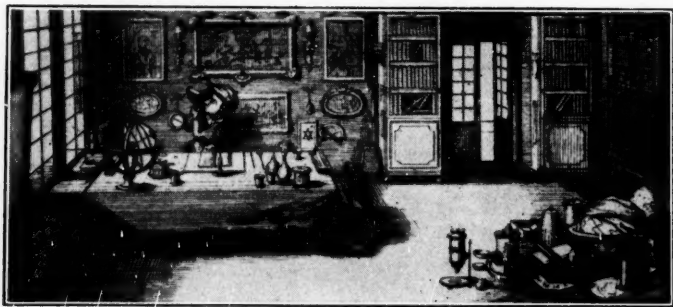


FIG. 9. An Early Eighteenth Century Laboratory. Joblot, 1718.

Leeuwenhoek, as we know, ground his own lenses and made his own simple microscopes, some 400 of them. In his hands the single lens reached *per saltum* the climax of its productivity, with in some cases a magnification of 200-300 diameters. This was while his contemporaries were depending chiefly upon compound microscopes, clumsy in construction and in most cases less efficient, though improvements on the type of instrument for which the term

"microscope" was coined by Giovanni Faber in 1625—a term that survived "smicroscope," "engyscope," etc. The chief contributions to the efficiency of the microscope during the period were made by Fontana (1646), Divini (c. 1648), Campani (c. 1660) and Hooke (1665) and gradually led to the ascendancy of a bilenticular system over the simple lens. Hooke is often credited with adding the field-lens to the ocular, but Monconys and Huygens, his contemporaries, preceded him in employing a plano-convex field-piece and a plano-convex eyepiece. At all events, the microscope remained for more than a century optically about as Hooke left it, while the rest of the instrument and its accessories advanced.

However, Bonanni (1691) knew much of what was needed, for he says he aimed at "an easy motion in examining the object; a convenient method of focussing; gradual focussing without the risk of losing sight of part of the object . . . ; an even illumination of the whole field; and a stable machine so that the eye can easily be replaced and see the object in the same place and light in order to draw it conveniently." And a decade later James Wilson (1702), emphasizing technique, expressed the opinion that "the late improvements made by magnifying glasses are not so much owing to the making them and composing microscopes, as the methods of applying objects for the advantage of light." Thus the microscope and its accessories at the beginning of the nineteenth century were born by the trials and errors of the eighteenth century instrument makers; in particular, John Marshall, a contemporary of Bonanni, and later Edmund Culpeper, Benjamin Martin and George Adams, Senior and Junior, won for English microscopes a high reputation. (Disney, Hill and Baker, 1928; Whipple, 1930; Clay and Court, 1932.)

The problems of chromatic and spherical aberration gradually became increasingly troublesome with higher magnification, involving lenses of shorter focal length and more nearly spherical form, but they were not successfully

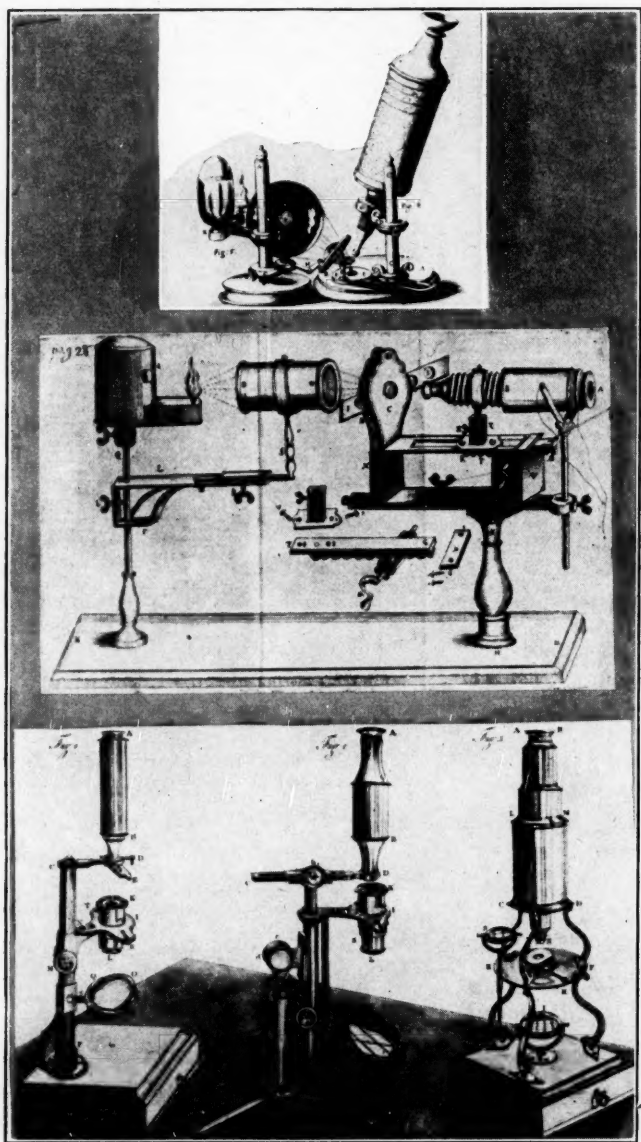


FIG. 10. Hooke's Microscope, 1665. Bonanni's Microscope, 1691. Types of Microscopes at the Close of the Eighteenth Century, Adams, 1787.

attacked until 1812 by Amici, who also apparently discovered the principle of the water immersion lens. In passing, however, it is interesting to note that Hooke (1678), while verifying Leeuwenhoek's animalcules, said, in effect, "that if you would have a microscope with one single refraction, and consequently capable of the greatest clearness and brightness, spread a little of the fluid to be examined on a glass plate, bring this under one of the globules, and then move it gently upward till the fluid touches and adheres to the globule."

The microscope itself, although the chief, was only one of many factors that contributed to the development of the technique of students of the "infinitely small." Methods for preparing objects to be examined played an indispensable part in unravelling the intricacies of the structure of plants and animals. It will be recalled that Hooke's success in resolving cork into cells was attained only when with "some further diligence" he cut off "an exceedingly thin piece of it"—probably the first reference to section cutting. Furthermore, Hooke later says that there are parts of animal and vegetable bodies "which cannot be well examined unless they be made to swim in a liquor proper and convenient for them," but if they "be put into a liquor, as water or very clear oyl, you may clearly see such a fabrick as is truly very admirable, and such as none hitherto hath discovered that ever I could meet with." This is apparently the first statement of the so-called wet preparation, a method that did not come into general use until the first quarter of the nineteenth century.

Leeuwenhoek, using simple microscopes, attached the specimen to a needle object-holder by glue, either directly or within a tiny glass tube in the case of liquids such as blood or infusion. "I did myself prepare," he says in 1674, "divers sorts of very slender, hollow glass pipes of which some were not thicker than a man's-hair." However, when occasion demanded, he used much larger tubes which he held by hand or clamped before the lens. Hooke

in his successful attempt to verify Leeuwenhoek's animalcules hit upon the basic principle of the transparent slide and coverglass preparation. "I take," he says, "instead of a glass pipe a very thin plate of Muscovy glass . . . and upon that I spread a very little of the liquor to be examined." And further, "All such bodies . . . whose surfaces are irregular . . . ought to be reduced to smoothness before they can be well examined." To accomplish this he put the material between two pieces of "very clear and thin looking-glass plate, very smooth and plain on both sides, and clean from foulness," and then pressed the preparation to make it very smooth and thin so that, for example, in the case of blood, no longer do "the multitude of those little globules confound and thicken the liquor so that one cannot perceive anything . . ."

Leeuwenhoek's other contemporaries using compound microscopes are reticent about their methods. To the best of my knowledge, Malpighi is silent on the subject, while Grew (1682b) merely states that it is necessary to study the anatomy of vegetables "by several ways of section, oblique, perpendicular, and transverse; all three being requisite, if not to observe, yet the better to comprehend, some things. And it will be convenient sometimes to break, tear, or otherwise to divide, without a section. Together with the knife it will be necessary to joyn the microscope; and to examine all the parts . . ."

Maceration of material, particularly plant tissues, one might suppose would have been hit upon early in preparing objects for the microscope, but it appears not to have been a generally recognized method before Moldenhawer in 1812, according to Sachs (1890), introduced this "important practical improvement" in technique. As a matter of fact, nearly a half century before, Hill had exploited maceration in his treatise on *The Construction of Timber*. Indeed, Benjamin Martin in 1742 suggested maceration to remove the epidermis of a leaf, but Hill used a much more elaborate method and first applied it to the

study of wood. Hill says that after several weeks' immersion, "by degrees, the parts loosen from one another; and, by gentle rubbing in a basin of water, just warm'd, they will be so far separated, that a pencil brush will perfect the business, and afford pieces of various size, pure, distinct, and clean."

Turning to the fixation and preservation of material for later study, again Hill (1770) was a pioneer. For example, he says:

Dissolve half an ounce of alum in two quarts of water; drop the pieces . . . for a few moments, into this solution; then dry them upon paper, and put them up in vials of spirit of wine. Nothing but spirit of wine can preserve their tender bodies; and till I found this method of hardening them first, that liquor often destroys them.

The origin of staining technique is difficult to determine, but if one follows Holzner, then Sarrabat in 1733 and Reichel in 1758 deserve priority. However, it seems not to be clear that they employed the dyes for microscopic purposes; merely observing the rise of solutions in twigs dipped into them (Smith, 1915a). But there is no question that Hill proceeded from maceration and fixing to true staining in his study of stems and thereby demonstrated structures otherwise invisible under the microscope. He used an alcoholic tincture of cochineal with considerable success and noted that since the stems of different species were not all stained the same, although the stain itself was the same, it must be "the construction of the body itself could in one instance have admitted it through passages which were closed to it in the other."

Equally interesting is another method described by Hill because it involved mordanting. He placed macerated twigs in a solution of sugar of lead and after two days transferred the material to a solution of quick lime, when, as he says, "the colourless impregnation . . . becomes a deep brown." Unless feeding Infusoria with colored material by Gleichen in 1778 and Ehrenberg in 1838 to show their internal structure is to be regarded as staining, there is apparently no further reference to such



technique until after the cell theory. Recently a botanist has justly stated that, "the great originality which John Hill showed in the manipulation of material . . . has not been given due credit" (Smith, 1915b; Conn, 1928, 1933.)

The modern microtome's history begins at least as early as Hooke's "penknife" and Leeuwenhoek's "sharp shaving razor," some of the sections cut with the latter being extant to-day. Before this it seems that no one had thought of section cutting, so all objects, unless naturally transparent, were viewed by reflected light. And little improvement in the tool was made until over a century later when "cutting engines" were developed to supply still thinner sections. One of the earliest machines was devised by Cummings and exploited by Hill in his study of wood. The invention has been ascribed to the Senior Adams, the well-known London maker of scientific instruments, but he does not mention it in the fourth edition of his *"Micrographia Illustrata"* that appeared a year later, in 1771. At all events, from this period on some sort of an "engine" was available for cutting sections as thin as "the two thousandth part of an inch," chiefly of plant tissue since embedding was of the distant future, but it was not until about 1860 that section cutting began to come into general favor with microscopists. (Fig. 11.)

Indeed, all microscopical technique was in its infancy not only during the period immediately preceding, but also long after that of Schleiden and Schwann. However, in spite of the backwardness of technique, the microscope itself had reached a degree of development that afforded unrealized potentialities. This is evident when we recall that, specifically with regard to the cell, botanists knew little more than that it consisted of a resistant wall with somewhat ill-defined contents, and zoologists with more difficult material were still more indefinite, although both were carrying on innumerable researches that threatened to swamp the science in minutiae. Unlimited complexity had supplanted apparent uniformity.



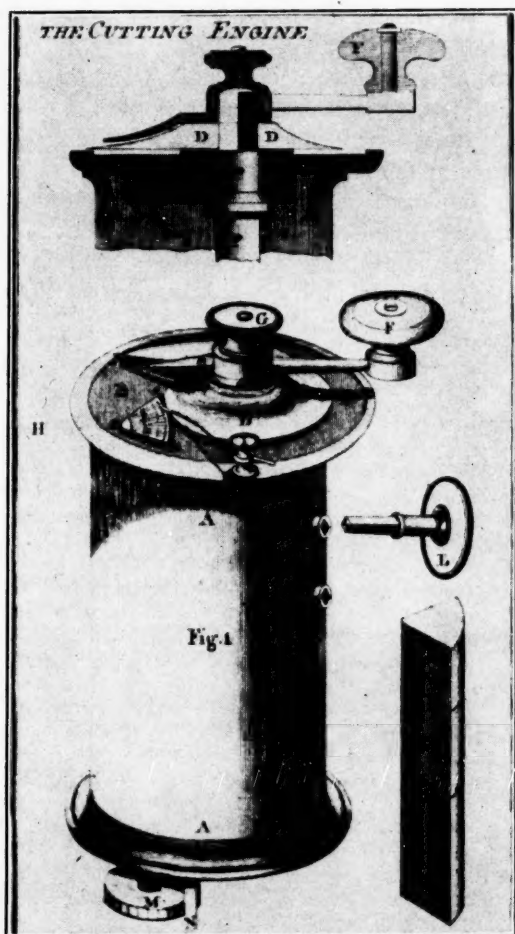


FIG. 11. Cummings' Cutting Engine. Hill's "Construction of Timber," 1770.

But the science was about to rise above the conceptions of Malpighi, Grew and Leeuwenhoek—Wolff was still unappreciated—and undergo the throes of a new birth. Just beginning were the significant investigations of Mirbel and

others, which during the following three decades laid the immediate foundations for—in fact, partly anticipated—the contributions of Schleiden and Schwann that were destined to pass the spark and precipitate the cell theory. It is not without significance that Huxley (1853), over ten years later under the impact of the theory, felt that Schleiden and Schwann had “grouped together an immense mass of details in a clear and perspicuous manner. Let us not be ungrateful for what they brought. If not absolutely true, it was the truest thing that had been done in biology for half a century.”

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## SCHLEIDEN'S CONTRIBUTION TO THE CELL THEORY

PROFESSOR JOHN S. KARLING

It is not an exaggeration to say that of all biological concepts none has proven more significant and fruitful of results than the cell theory which gradually emerged during the early part of the nineteenth century. Biologists are now agreed that the formulation of this doctrine marks an epoch in biological science and that in its far-reaching influence on research the cell concept merits a position beside the atomic theory and the doctrines of organic evolution and Mendelism. The enunciation of this concept and the realization that all plants and animals are composed of cells which are essentially alike in their make-up and formed in the same fundamental manner by division and that the activity of the organism is the sum total of the activities, interrelations and interactions of its individual cells, opened up horizons whose limits and possibilities have not yet been exhausted or even fully realized. The cell concept is the concept of life, its origin, its nature and its continuity.

Important and significant as the cell theory has proven to be, it is all the more a paradox of history that the two biologists who added little if anything new or original to this theory are now quite generally regarded as its founders. Nowhere is the paradox better illustrated than in the past, and current text-books of botany, zoology and biology which discuss the history of the cell theory. Of those which treat of this subject at all, 98 per cent. state almost unequivocally that Schleiden and Schwann originated the idea that all organisms are composed of cells which are formed in the same fundamental manner. This is also the belief expressed by the majority of text-books on cytology. Only two of the current texts, as far as I am aware, attempt to show that the cell concept was the cumulative result of a large number of investigations in the

early part of the nineteenth century. The belief that Schleiden and Schwann were the founders of the cell theory is so commonly taught in our high schools and universities that biology students are led to believe that, to use the words of Rich, "the idea sprang Minerva-like, fully formed and original from the substance" of their brains. Nothing could be farther from the truth, as a few of the more historically-minded biologists have pointed out from time to time.

It is thus proper and fitting on the occasion of this so-called "Centennial of the Cell Theory" that we refute again this erroneous conception and review anew the steps in the gradual development and emergence of the cell theory. What I shall here present on the relation of Schleiden to the cell theory is not essentially new and original. In 1879 and 1892 Hertwig reviewed to some degree the contributions of the early phytotomists and pointed out that the cell theory had its origin in study of plant anatomy. In 1907 Heidenhain gave a brief account of the development of the cell concept in his "Plasma und Zelle," while in the third editions of their text-books, Wilson and Sharp review the history of this subject at some length. Wilson, however, says, "Schleiden and Schwann are universally and rightly recognized as the founders of the cell theory." Gerould and Rich, in particular, have clearly emphasized the contributions of Dutrochet and pointed out that he formulated the cell concept a decade and a half before Schleiden and Schwann. It is also of interest to note here that the essential historical idea to be presented in this paper has been taught by Professor R. A. Harper for more than thirty years in his cytology classes at the University of Wisconsin and Columbia University.

Turning now particularly to Schleiden and the part which he played in the formulation of the cell concept of 1838-39, we can confine ourselves to his "Contributions to Phytogenesis," since this is his only paper which relates directly to the subject. In this contribution, which was



first communicated to Schwann in October, 1837, and published in Part II of Müller's "Archiv" in the following year, Schleiden makes these significant statements:

But every plant developed in any higher degree, is an aggregate of fully individualized, independent, separate beings, even the cells themselves. Each cell leads a double life: an independent one, pertaining to its own development alone, and another incidental, in so far as it has become an integral part of a plant. It is, however, easy to perceive that the vital process of the individual cells must form the very first, absolutely indispensable fundamental basis, both as regards vegetable physiology and comparative physiology in general. . . .

And further as relates to the origin of new cells, Schleiden proceeds at once to the wholly false idea of cell formation by a sort of crystallization about a granule. He says:

. . . Minute mucus granules are very soon developed in the gum, upon which the solution of gum, hitherto homogeneous, becomes clouded, or when a large quantity of granules is present, more opaque. Single, larger, more sharply defined granules next become apparent in the mass; and very soon afterwards the cytoblasts appear, looking like granulous coagulations around the granules. So soon as the cytoblasts have attained their full size, a delicate transparent vesicle rises upon their surface. This is the young cell, which at first represents a very thin segment of a sphere, the plane side of which is formed by the cytoblast, and the convex side by the young cell, which is placed upon it somewhat like a watch-glass upon a watch. . . . The entire cell then increases beyond the margin of the cytoblast, and quickly becomes so large that the latter at last merely appears as a small body enclosed in one of the side walls.

It is an altogether absolute law that every cell (setting aside the cambium for the present) must make its first appearance in the form of a very minute vesicle, and gradually expands to the size which it presents in the fully formed condition.<sup>1</sup>

A careful analysis of these statements shows that they include three fundamental premises, the first two of which are but briefly mentioned and implied, while the third is developed at great length. These premises are: first, *the recognition of the fact that plants throughout are composed of independent cells, which are the units of structure, physiology and organization*; secondly, *the duality of cells—their independent existence pertaining to their own development, and another as an integral part of the plant*;

<sup>1</sup> Translation by Smith.

and, thirdly, *that there is one general and common law of cell formation*. As has been noted above, the first of these premises is only incidentally mentioned by Schleiden. As to the second—the duality of the cell—it is but briefly stated. Historians, none the less, are inclined to credit the first tacit recognition of this fact to Schleiden. The third proposition relating to the law of cell formation is the main thesis and comprises all but a few pages of his contribution.

Having thus noted the fundamental propositions included in Schleiden's paper, and inasmuch as he does not give specific recognition to the discoveries of previous investigators, it is necessary that we make a critical survey of the literature prior to 1838 to determine whether or not these propositions are his own contributions to the cell concept. Many of the papers to be cited in this survey include much that is irrelevant and erroneous, but I shall refer only to that which relates directly to the development of the cell theory. Doubtless many fundamental contributions have been overlooked and omitted in this analysis, but sufficient literature has been examined and studied to indicate clearly Schleiden's relation to the cell theory. That plants are composed of cells had been known since the discoveries of Hooke, Grew, Malpighi, Leeuwenhoek and Hill in the seventeenth and eighteenth centuries, but it was not until the first quarter of the nineteenth century that the cell began to be regarded as the fundamental living individual unit as well as the structural element of all plant tissues. Mirbel and Sprengel (1802), Bernhardt and Link (1805) and Rudolphi (1807) recognized the cell as one of the units of structure in most plants, but they made a distinction between it and the elongated vessels present in the mature tissues. Sprengel at this early date, none the less, hints at the idea of a similarity in cellular structure of plants and animals when he says: "As far as I know at present . . . the nature of plants as well as animals appears to consist in the formation of a tissue, which we

can best compare to the cells of a honey comb, and, to be brief, call cellular tissue." He did not, however, regard the cell as a separate independent unit with a wall entirely its own. In 1806 Treviranus showed that elongated pitted vessels are formed by the disappearance of oblique cross walls, and in a like manner derived the true spiral vessels from long thin-walled cells. Thus was demonstrated for the first time that elongated vessels are also nothing but modified cells, but the significance of this discovery was not clearly realized until it had been confirmed by von Mohl in 1831 and Mirbel in 1833.

In 1802 Mirbel published his "*Traité d'anatomie et de physiologie Vegetales*," in which he states that, "Plants appear to be entirely composed of cells and of tubes, all parts of which are continuous." Like most phytotomists of that period, he made a clear distinction between cells and tubes, but in the second edition of his work in 1809 he omits tubes from the aphorism noted above. Mirbel more than any previous phytotomist insisted that all forms of plant structures are developed from cellular tissue. Simultaneous with Mirbel's second edition appeared Lamarck's (1809) "*Philosophie Zoologique*," in which he extends the concept of the cellular tissue as being the structural and organizing unit to both plants and animals, saying:

No body can possess life if its containing parts are not of cellular tissue, or formed by cellular tissue. Thus every living body is essentially a mass of cellular tissue in which more or less complex fluids move more or less rapidly; so that, if this body is very simple, that is, without special organs, it appears homogeneous, and presents nothing but cellular tissue containing fluids which move slowly within it; but if its organization is complex, all its organs without exception, as well as their most minute parts, are enveloped in cellular tissue, and even are essentially formed of it.

In the second volume he devotes a whole chapter to cellular tissue and adds further:

It has been recognized for a long time that the membranes that form the envelopes of the brain, of nerves, of vessels of all kinds, of glands, of viscera, of muscles and their fibers, and even the skin of the body, are in general the productions of cellular tissue. However, it does not appear that anyone has seen in this multitude of harmonizing facts anything but

the facts themselves; and no one so far as I know, has yet perceived that cellular tissue is the general matrix of all organization, and that without this tissue no living body would be able to exist nor could have been formed.

In a footnote to this chapter Lamarek states that he has taught this principle in his classes since 1796.

It is to be noted, however, that Mirbel and Lamarek did not regard the individual cell as the unit of structure and organization. To them, the continuous membranous cellular tissue rather than the cell is the elementary structure from which development proceeds. Lamarek, none the less, must be recognized as having pointed out once more the similarity of fundamental structure in plants and animals, although his interpretation may be somewhat incorrect.

Shortly afterward, Treviranus (1811) in a reply to Mirbel showed, as Malpighi (1675) and Link (1809) had done, that cells could be readily isolated as units by maceration, and particularly stressed the vesicular character of plant cells. This idea that the cell is an independent and individual unit as far as its own structure is concerned was confirmed by the studies of Moldenhawer in 1812 in which he employed the maceration technique very extensively. By this method he showed clearly that parenchyma cells and elongated vessels are closed sacs and tubes with walls of their own rather than open spaces in a membranous tissue.

These early studies may be said to have paved the way for the outstanding study and brilliant generalization of Dutrochet in 1824, who may well be called the forgotten man of the cell theory. By boiling plant and animal tissues in nitric acid and water, he isolated the cells as distinct entities with their own walls and contents, and this led him to the generalization that "the cell is the fundamental element of organization." In 1824 he published the little book entitled "*Anatomical and Physiological Researches on the Intimate Structure of Animals and Plants, and Their Motility*" in which we find as definite and clear an enunciation of the cell concept as that formulated in 1838

and in 1839. Inasmuch as Dutrochet will doubtless be discussed in detail by other speakers on this program, I shall confine myself largely to his botanical statements and their relation to Schleiden's ideas:

I must repeat here that which I have stated above regarding the organic texture of plants: we have seen that plants are composed entirely of cells, or of organs which are obviously derived from cells; we have seen that these cells are merely contiguous and adherent to each other by cohesion, but that they do not form a tissue actually continuous. . . . All the organic tissues of plants are made of cells, and observation has now demonstrated to us that the same is true of animals. . . . One can therefore draw the general conclusion that the globular corpuscles which make up all the organic tissues of animals are really globular cells of extreme smallness, which are united only by cohesion. Thus all the tissues, all the organs of animals are really only a cellular tissue diversely modified. This uniformity of ultimate structure proves that organs really differ from the other only in the nature of the substances which are contained in the vesicular cells of which they are composed.<sup>2</sup>

Here we have for the first time, as far as I am aware, a demonstration by observation of the lucky guess or hypothesis which Oken made in 1805 and 1810 when he said, "animals and plants are throughout nothing else than manifoldly divided or repeated vesicles." Dutrochet's confirmation of this hypothesis and his clear-cut expression that plants and animals throughout are composed of cells was made almost a decade and a half before Schleiden and when Schwann was but a lad of 14 years. While it is true that Dutrochet did not recognize as clearly as his successor Meyen that the cell has its own life cycle, that he failed to observe the nucleus, and had little knowledge of the inner structure of cells, he none-the-less recognized the independence and individuality of these units as well as their relation to the structure and organization of the plant and animal as a whole. His generalization as to the fundamental nature of all organisms becomes all the more impressive in comparison with those of Schleiden and Schwann when we consider the inadequacy of the microscope of 1824 and the fact that he did not have the excellent and meaty discoveries of Meyen, von Mohl, Brown, Müller, Valentin, Henle, Purkinje, and others to draw on. As one

<sup>2</sup> Translation by Rich.

reads Dutrochet's contribution more extensively, one can not escape the feeling that we are perhaps fifteen years too late in our "Centennial of the Cell Theory," and that future generations will regard this celebration as a humorous incident of the strange way in which science makes progress.

Dutrochet likewise recognized the cell as the physiological unit and thus antedates Meyen, von Mohl, Raspail, Schleiden and other phytotomists in this respect also. He adds:

It is within the cell that the secretion of the fluid peculiar to each organ is effected. . . . Thus the cell is the secreting organ par excellence. It secretes inside itself, substances which are, in some cases, destined to be transported to the outside of the body by the way of the excretory ducts, and, in other cases, destined to remain within the cell which has produced them. . . .

In this connection it is also well worth while to note another contribution of Dutrochet, a restatement of which brought Schleiden great renown fourteen years later as its originator. In his treatment of cell formation Schleiden discusses at great length the question as to what constitutes growth, and in conclusion he lays down three principles which are commonly taught to-day. Growth, to him, consists, first, of the formation of new cells; secondly, of the expansion or enlargement of cells; and thirdly, of a thickening or lignification of their walls. With his usual arrogance Schleiden announces these principles as his own by the statement "that, in respect to scientific botany, the idea (to) grow still requires a new foundation in order to be capable of being applied with certainty." With this in mind, let us now turn to Dutrochet. "Growth," he says, "results both from the increase in the volume of cells, and from the addition of new little cells. It is therefore, evident that new, rudimentary cells are formed, which, by increasing in size, finally become cells such as those which have preceded them in order of appearance and development." Dutrochet elaborated this principle further and discussed growth at great length in his extensive memoir in 1837, and if Schleiden had taken the trouble



to familiarize himself with the botanical literature of the time, he would have found his ideas concerning growth clearly expressed and elucidated. Perhaps he was familiar with Dutrochet's contribution but deliberately stated the latter's ideas as his own.

The individuality of the cell as a structural and physiological unit was again pointed out and emphasized in 1828 by Meyen in his booklet on "Anatomical-Physiological Researches on the Content of Plant Cells."

"The cells of plants," Meyen says, "are to be regarded therefore as single, independent individuals, small plants as it were in the larger, each of which carries on its own life independent of its surroundings. The mechanism, however, becomes more complex by their aggregation into groups, whereby the nature of the plant is heightened. . . . Cells are the organs of the plants which take up the raw (humors) substances for the nutrition of the same." Here we have the clearest expression so far of the conception that the cell is the unit of life—perhaps the only unit of life. The multicellular organism is an aggregate; its unity is due to the interrelations and interactions of cells. This concept of the organism as a mass of cells which integrate and interact to form a coordinate whole is perhaps the real climax of the cell theory.

Outside of its relation to the independence and individuality of the cell, this book by Meyen, written when he was but twenty-four years old, is particularly significant in relation to the more modern cell theory, because it deals almost exclusively with the content of the cell, to which latter was given the name protoplasm. While many of his ideas were incorrect, he nevertheless focused particular attention on the more viscid, vital elements of the cell rather than on the cell wall, and he is thus to be regarded as one of the forerunners of the protoplasm doctrine. A year earlier (1827) he had described and figured very accurately the nucleus in *Spirogyra princeps*, but the significance of this discovery was obscured by his fanciful belief that the nucleus gives rise to infusoria as the algal fila-

ments decay. In 1830 he published his text-book on phytotomy, in which occurs the oft-quoted passage relating to the cell:

Plants appear either singly so that each forms an individual as in some algae and fungi, or they are united in greater or smaller masses to form a more highly organized plant; even here each cell forms an independent isolated whole; it nourishes itself, it builds itself up, and elaborates the raw nutrient materials, which it takes up, into very different substances and structures.

Here we have a statement of the character and inter-relationship of the cell that is so true and modern that it may well have been uttered to-day. In it occurs not only the doctrine of the independence and individuality of the cell, but its duality as well. The cell, according to Meyen, not only leads an independent existence relating to its own life but plays an integral part in the organization and development of the whole plant. To Meyen, as we have already noted above, the higher plant or organism is but an aggregate or colony of individual cells—a statement which Schleiden and Schwann emphasized so strongly in their contribution, without acknowledging its authorship. It may well be noted here, however, that this idea itself is by no means original with Meyen. Twenty-three years earlier the naturalist and philosopher Lorenz Oken (1805) made the following statement as to the nature of plants and animals, which has already been noted above: “. . . Animals and plants are throughout nothing else than manifoldly divided or repeated vesicles.” Again in 1810 he says, “In so far as the plant is a multiplication of primitive vesicles, it consists of cellular tissue.” And finally several years later (1835) he amplifies this idea as follows: “The ground work of all plant and animal substances consists of delicate vesicles, . . . The lowest plants like the fungi . . . and algae . . . are nothing more than such vesicles which appear singly or grown together. The cellular tissue of plants is therefore nothing more than an aggregation of primitive plants. The same meaning applies to the cellular tissue of animals.” Turpin also had expressed this idea as early as 1825.

While it is true that Oken's statements were not based on observations and facts and seem to be nothing more than a fortunate guess or hypothesis, the idea is nevertheless clearly expressed, and he must be given serious consideration as foreshadowing the cell concepts expressed by Dutrochet and Meyen and later restated by Schleiden and Schwann.

Returning again to Meyen, the significance and value of his discoveries and generalizations are unfortunately obscured by his insistence that elongated vessels and latiferous ducts were elementary organs in addition to cells. He retained this idea of the latex vessels as late as 1837, which leads one to suspect that even at this date he was not completely certain of the cell as a universal elementary structural unit.

This brief survey of the literature shows clearly that the first two premises of Schleiden—the doctrine of the cell as an independent, individual, structural and physiological unit, and its dual existence—had been clearly stated and demonstrated several times prior to 1838, and it is thus apparent that Schleiden added nothing new or original in the opening paragraphs of his "Contributions to Phytogenesis." It is true that he does not definitely claim these ideas are his own, but his failure to recognize the contributions of other investigators puts him at once in the class of the borrowers rather than that of the original investigator.

Turning now to the third and major premise of Schleiden's contribution—namely, that there is one "universal law for the formation of the vegetable cellular tissue in the Phanerogamia," we find that it is true only in statement and completely false as to the method of accomplishment. All biologists are now agreed that there is but one method of cell formation, but that it occurs by division of a preexisting cell—not by the aggregation of mucus granules in the cytoplasm to form first a nucleole and cytoblast and then the cell. This fantastic and completely erroneous idea of cell origin was regarded by Schleiden as the

most important and fundamental part of his contribution, and on this he laid the greatest stress. The first two propositions noted above were but introductory to this major premise.

If we examine again the literature closely in relation to the origin of cells, we find that Schleiden's false theory is not original but merely a modification of an old theory of the early phytotomists which was also rather widely held by zootomists of that period. At that time there were two outstanding views as to how cells arise: first, the view of the zootomists and phytotomists that the nucleus and cell develop from an aggregation and confluence of granules of various sorts in the viscid content of the cell; and secondly, the view of numerous phytotomists that new cells arise by division of a preexisting cell. None of these theories, however, had been extended to all plant and animal cells and formulated as a universal law of cell formation. The first view seems to have arisen from the old theory of Sprengel that new cells are formed by the expansion and vesiculation of granules and bodies in the cell. In 1802 Sprengel proposed this theory as follows from his microscopic study of bean seeds:

If you examine a bean before it germinates, you will observe in the hollow parts no specific form, no regular structure; one grain close by another. . . . The bean now germinates: the two cotyledons between which the embryo is enclosed swell: the skin loosens. If you take a very delicate, completely transparent section from the cotyledons you become aware of an aggregation of small vesicles intermingled with the moisture, which, in my opinion, can be called the true rudiments of the cellular structure. The more the plant expands the more regular, cell-like, and continuous this tissue becomes. . . . The delicate vesicles, which are yet swimming about in the moisture, appear to have the ability to become cells, and are perhaps in succession transformed into such. In a similar manner, you will note, all other plants originate from seeds. The irregular, unorganized chaos of dry seeds takes on a regular structure, while through the imbibition of moisture vesicles develop, which, crowded and expanded within and without by sap and confined by adjacent vesicles, assume a definite angular shape. . . .

These granules which Sprengel described as vesiculating to become cells are now recognized starch and aleurone grains. His theory in modified form was later adopted by Treviranus, Rudolphi and Kieser, and they extended it

to involve a wide variety of granules in the cell. Eventually, it appears to have been taken over by the zootomists, who further modified and adapted it to fit the more recently discovered data from animal tissues. Schleiden distinctly rejects Sprengel's theory, but after all, there is very little fundamental difference between the idea of cells originating by the swelling of starch grains and by the vesiculation of mucus granules or cytoblasts. I shall here refer to a few of the descriptions of cell origin in zoological literature to show the relation of these views to Schleiden's idea of cell formation.

In 1830 Baumgartner described the formation of red corpuscles by the aggregation and condensation of granules in the blood serum. In 1836 C. H. Schultze confirmed the observations of Baumgartner and described nuclear and cell formation in the blood of amphibia and fish as follows:

The true nuclei are formed in the following manner: the corpuscles which are becoming flattened always have in the beginning two or more yolk granules, or sometimes whole masses of smaller ones. Out of those are formed the nuclei, either by the fusion of numerous small ones to form a larger granular nucleus, or by the gradual disappearance of the smaller granules until a single large one remains. . . . On the other hand, in *Perca fluviatilis* and *Cyprinus erythrophthalmus* I find that the nuclei are more often the primary structures and are formed from the transformation of yolk granules, and that the lens-shape vesicles later arise around these.

In the same year Valentin (1836) figured the same type of cell formation in pigment cells, and in 1837 Wagner demonstrated its occurrence in the ovum. In these and the older contributions of the phytotomists seems to lie the kernel of Schleiden and Schwann's peculiar conception of nuclear formation in the cytoplasm and the subsequent development of cells around the cytoblast. Their figures of the process are so fundamentally similar to those of Schultze and Wagner that they may well have been based directly upon them. As a matter of fact, Schwann cites Wagner's figures in his supplement as a confirmation of his observations. Erroneous and fantastic as Schleiden's idea of cell origin in embryonic tissues was, he far sur-

passed it in imagination when he came to describe cell formation in the cambium of woody stems. Here he abandons his previous idea of cell formation and proposes a theory of simultaneous and spontaneous generation of cells from an unorganized fluid:

Here, so far as we are at present acquainted with the subject, there is no formation of cells within cells, here no expansion of all sides of the originally minute vesicle occurs, there is here no cytoblast upon which the young cell might be developed; but beneath the outermost layer of cells, which are comprised in the term bark, an organizable fluid is poured out, as it were, into a single, large intercellular space, which fluid, as it seems, consolidates quite suddenly throughout its entire extent into a new, altogether peculiarly-formed tissue of cells, which are deposited one upon another, the so-called prosenchyma. Here, moreover, there is decidedly no formation of vascular bundles from cells of lower order, for all of them originate simultaneously and of their full size; and what has been called (spiral) vessels of the wood, is something which differs immensely from the spiral vessels of herbaceous plants, both in respect of their origin, and probably of their physiological significance also.

That is Schleiden's idea of cell formation in the cambium and secondary thickening in woody plants—purely a hypothesis spun out of thin air.

How unfortunate for biological research of that decade and the reputation of Schwann that Schleiden did not choose the alternative and correct view of his contemporary botanists! It had been shown again and again before 1839 that new cells are formed by the division of preexisting ones. In 1830 Morren clearly described the origin of new cells by division in the alga, *Crucigenia*; Dumortier figured and described division again briefly in *Cladophora* in 1832, and in 1833 Mirbel observed its occurrence in the spores of *Marchantia*. In 1835 Winter, under the direction of von Mohl, published a long dissertation entitled "On the Multiplication of Plant Cells by Division," in which he showed for the first time the successive stages of cell division in *Cladophora*. Von Mohl republished this paper as his own in 1837 and again in his "Vermischte Schriften" in 1845 without mentioning Winter's name, which leads us to suspect that he made the original discovery and possibly wrote Winter's thesis. This paper



was followed in 1836 by another contribution by Morren on division in *Closterium*, and in 1837 he gave a brief summary of the discoveries of cell origin by division of a pre-existing cell in which he says that "the succession of these observations will suffice without doubt to establish this fact (cell origin by division) as one of the most established of vegetable organogenesis." In the same year Dumortier reported that the cellular tissue of the liver of molluscs and gastropods originated by division of preexisting cells in the same manner as he had described for *Cladophora* five years earlier. In 1838 Mohl described the origin of the guard cells of stomata by division, and in the same year Meyen reported the occurrence of cell division in *Scenedesmus* and the corticating cells of *Chara*. In this volume on plant physiology Meyen declared that cell division was a common occurrence in filamentous algae, fungi, and the Characeae. He followed this in 1839 with another paper on division in the embryo sac of *Viscum*, the spore mother cells of *Trichoslylium*, the guard cell rudiments of stomata in *Hyacinth* and the vegetative cells of *Merismopedia* and *Ceramium*. In the same year Mohl described and figured in considerable detail division of the spore mother cells of *Anthoceros*, and showed the presence of fibers between the divided plastids which are now generally recognized as the rudiments of the achromatic spindle figure.

Numerous as these observations were, however, none of the investigators recognized the universality of cell division or formulated a general law of cell formation, or showed the relation of the nucleus to cytokinesis. There were at hand, none the less, numerous data, descriptions and figures on the correct method of cell origin which Schleiden and Schwann might have utilized. Schleiden, in his profound ignorance or disdain of the contributions of others, disregarded them completely, while Schwann, although apparently familiar with some of them, did not regard these discoveries as being of much significance.

The immediate effect of Schleiden's error was to place

a false emphasis on the erroneous distinction between endogenous or free cell formation and cell division, and it was not until after many years of study that microscopists realized that the two methods are fundamentally identical.

It is thus obvious from this survey that all the facts and hypotheses as well as misconceptions included in Schleiden's paper are to be found in biological literature prior to 1838 and that even unto the errors and inaccuracies he added nothing new or original. Schleiden's misleading theory nevertheless focused attention on the wide prevalence of nuclei in plant cells and their possible relation to cell formation, and this seems to be his primary contribution. It must be borne in mind, however, that his idea of this relationship was completely false and confusing and that he regarded the nucleus as being absorbed or disappearing after the new cell had been fully formed. The very enormity of his error coupled with the disdain he had for his contemporaries nevertheless stimulated others to study the nucleus with greater care, if for no other reason than to disprove Schleiden's theory. They were, consequently, led to the discovery that nuclear division usually precedes cell division. In the writer's opinion, therefore, it is doubtful that Mohl, Barry, Unger, Nägeli, Remak, Kölliker, Hofmeister and others would have directed their attention so soon to the relation of the nucleus to cell division had not Schleiden perpetrated his fantastic and erroneous idea. This error together with Schleiden's commanding position as a teacher proved thus to be a ferment of deep influence in revitalizing biological science. By their insistence on the study of the early developmental stages of tissues, Schleiden and Schwann brought about a marked change in attitude, and after 1838-1839 histology became very different from what it had been before. With the restatement and elaboration thus of Dutrochet's and Meyen's concepts of the cell in terms of the newly accumulated data, histologists, physiologists, pathologists and embryologists began to think primarily in terms of cells.

Does this critical appraisal of Schleiden's contribution

mean therefore that his name should be excluded from the cell theory and that Schwann stands alone as its founder? Certainly not. Except for his careful and accurate demonstration of the true cellular nature of numerous animal tissues, Schwann must stand or fall with Schleiden, because the most fundamental part of Schwann's theory—namely, that there is one fundamental principle of cell formation—was borrowed from Schleiden. All that Schwann knew and wrote in relation to the cellular structure of plants and the formation of cells came from Schleiden's paper, as he admits in his introduction. He adopted Schleiden's theory of cell origin completely, extended it to animal cells in which it had not previously been shown, and compared nuclear and cell formation to the development of crystals in a mother liquor. Schwann thus attempted to bridge, figuratively at least, the gap between the organic and inorganic. If we analyze further his interpretation and extension of Schleiden's theory, we find that it is also a repetition of the fundamental idea of Wolf's (1759) doctrine of generation, as Huxley (1853) has already pointed out. "The generation of cells," says Schwann, "takes place in a fluid, or in a structureless substance," the cytoblastema. Compare this with Wolf's statement:

Every organ is composed, at first, of a mass of clear viscous, nutritive fluid, which possesses no organization of any kind, but is at most composed of globules. In this semi-fluid mass cavities (Bläschen, Zellen) are now developed; these, if they remain rounded or polygonal, become the subsequent cells; if they elongate, the vessels.<sup>3</sup>

Schwann's conception is but a slight modification of this idea. Instead of operating in the organ as a whole, the generative activity of the structureless fluid is limited to the confines of individual cells, whereby new cells are formed within preexisting ones. It may well be noted in this connection also that the cellular nature of the chorda dorsalis, cartilage, epithelium, feathers, crystalline lens and adipose tissue, which Schwann described at length in the first part of his contribution, had previously been dem-

<sup>3</sup> Translation by Huxley.

onstrated by Muller, Purkinje, Henle (1838), Hooke (1665), Dutrochet (1824), Raspail (1837) and others. Furthermore, on several occasions Valentin had compared the cellular structure of several of those tissues to that of plants. What we have said previously about Schleiden's lack of originality and accuracy of interpretation may equally well be extended to Schwann. He makes no mention of Dutrochet and Meyen, but by comparing his text with that of Dutrochet, it is difficult to escape the feeling that Schwann was thoroughly familiar with the former's paper. Rich suggests that not only was he familiar with Dutrochet's work but that he may possibly have paraphrased certain passages of it.

As the falsity of Schleiden and Schwann's theory of cell formation was gradually demonstrated, this part of their contribution received less and less notice, and as time went on their fame came to rest primarily on the erroneous belief that they had been the first definitely to announce the doctrine of the independence, individuality and duality of the cell and that it is the elementary unit of organization and structure of all organisms. In the opinion of present-day biologists this stands as the essential part of their contribution. But, as we have emphasized above, it is by no means original. My study of the early biological literature, and I do not regard it as being very complete, leads me to these conclusions. The idea that plants and animals are an aggregate of similar, independent, individual units was first expressed as a philosophical speculation without much factual foundation by Oken in 1805 and 1810. It was restated and confirmed by clear-cut observation for the first time by Dutrochet in 1824, elaborated and extended for plant cells by Meyen in 1828 and 1830, and finally accepted by Schleiden and Schwann in 1838-1839. After the lapse of a century we are better able to judge the relation of Schleiden and Schwann to the history of the cell theory; and we can now realize that, as they themselves thought, their outstanding contribution was the false and wholly misleading attempt to compare cell formation with the formation of a crystal in a mother liquor.

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## PREDECESSORS OF SCHLEIDEN AND SCHWANN

PROFESSOR EDWIN G. CONKLIN

IN science no less than in the material universe it is difficult if not impossible to find the real beginnings of anything, for every event is the result of many preceding ones. In short, there is no creation *de novo* in either the material or the intellectual universe. In an extremely interesting article in the *Scientific Monthly* for December, 1937, entitled "Who Invented It?," S. C. Gilfillan lists the numerous reputed inventors of the telegraph, the friction match, the barometer, the telephone, the airplane, wireless, the steamboat and other modern inventions; and as to the ancient inventors of the wheel, the pulley, the boat, the sail, history is silent: yet in each and all of these inventions we may be sure that there were many cooperators. The fact is that all discovery and all science are social functions. Their progress is possible only by the conscious or unconscious cooperation of many minds.

These remarks apply with especial force to the origin of the cell theory. The present symposium was designed to mark the centenary of the cell theory of Schleiden and Schwann. We are accustomed to celebrate anniversaries of births, decades of science, jubilees of men and institutions, centuries of progress, millennia of world history. We pick out some event of 1838 and celebrate its centenary in 1938, as if it had no antecedents, as if it were a creation rather than an evolution.

The cell theory in its fundamental features is older than either Schleiden or Schwann. Their cell theory was a special and, in important respects, an erroneous one. There is no present biological interest in their theory, and it is amazing that we still continue to call it after them, as if they were its sole inventors, thus embalming the names of real scientists with one of their most serious blunders. It suggests the distinction conferred upon "Bahn" by an

English translation of the German phrase "Bahn-brechende Werke" as "The pioneer work of Bahn."

But mankind desires to concentrate honors on individuals, to pick out persons to love or hate or admire, rather than to deal with multitudes of persons or causes, and so we still speak of the cell theory as if Schleiden and Schwann discovered cells or first proposed that they are the universal units of organic structure and function. However, this is far from the case. As is well known, cells were first seen, named, described and figured by Robert Hooke, an English physician, mathematician and architect, 170 years before the work of Schleiden and Schwann. In 1667 Hooke published his "*Micrographia*," in which he described among many other things the little chambers or cells which he had seen with his microscope in sections of cork. In 1675 and again in 1679 Marcello Malpighi, an Italian anatomist, physiologist and physician, published two folio volumes which justifies his title of "creator of scientific botany." He distinguished parenchyma from fibrous tissue and air tubes from sap vessels. For the elements of the parenchyma he used the term "utriculi." Nehemiah Grew, English botanist and secretary of the Royal Society (1677), published his "Anatomy of Plants" in 1682, showing that the parenchyma of plants is composed of vesicles or closed spaces in a homogeneous ground mass.

During the next hundred years, several botanists and anatomists saw and figured the utricles or vesicles in plants and animals. The most notable of these was Caspar Frederick Wolff. His doctoral thesis for the M.D. degree was published in 1759 when he was only 26 years old; it was entitled "*Theoria Generationis*," and it marks an epoch in the study of the development of plants and animals. Wolff showed that in their development the parts of plants are composed of utricles, and "the particles which constitute all animal organs in their earliest inception are little globules which may always be distinguished under a microscope of moderate magnification." V.

Sachs in his "History of Botany" says that this was the most important work of the period between Grew (1682) and Mirbel (1802). "It was Wolff's doctrine of the formation of cellular structures in plants which was in the main adopted by Mirbel." (Sachs.)

For more than 100 years the words utricles, vesicles or globules were used to designate these constituent parts of animals and plants, and only in the beginning of the nineteenth century did Hooke's term "cell" again come into use. In 1808 and 1809 Brisseau de Mirbel, professor of botany in the Musée d'Histoire Naturelle in Paris, published a notable work on his theory of plant organization ("Theorie de l'organisation végétale"). The general conclusions of this work were that "The plant is wholly formed of a continuous cellular membranous tissue." In a set of "Aphorisms" that he had prepared to accompany a large plate illustrating the finer structure of plants he wrote, "Plants are made up of cells, all parts of which are in continuity and form one and the same membranous tissue." It is apparent from this that while Mirbel recognized the universal presence of cells in plants he also regarded them as bound together in a membranous tissue.

Professor John H. Gerould, in an important paper entitled "The Dawn of the Cell Theory" (*Scientific Monthly*, March, 1922), has shown that the great French naturalist, Lamarck, deserves to rank as one of the founders of the cell theory. In his "Philosophie Zoologique," published in 1809, he says: "No body can possess life if its containing parts are not a *cellular tissue*, or formed by *cellular tissue*." Again:

Thus every living body is essentially a *mass of cellular tissue* in which more or less complex fluids move more or less rapidly; so that if this body is very simple, that is without special organs, it appears homogeneous and presents nothing but *cellular tissue* containing fluids which move within it slowly; but if its organization is complex all its organs without exception, as well as their most minute parts, are enveloped in cellular tissue, and even are essentially formed of it.

In the second volume of his great work, "Philosophie Zoologique," Lamarck devotes an entire chapter to cellular tissues, in which he says:

It has been recognized for a long time that the membranes that form the envelopes of the brain, of nerves, of vessels of all kinds, of glands, of viscera, of muscles and their fibers, and even the skin of the body are in general the productions of *cellular tissue*. However, it does not appear that anyone has seen in this multitude of harmonizing facts anything but the facts themselves; and no one, so far as I know, has yet perceived that *cellular tissue* is the general matrix of all organization, and that without this tissue no living body would be able to exist nor could have been formed. Since the year 1796 I have been accustomed to set forth these principles in the first lessons of my course.

Everywhere Lamarck speaks of *cellular tissue*, and apparently neither he nor Mirbel thought of the cell as an independent unit. This idea was more clearly expressed by Dutrochet, a French physiologist and physicist, in 1824 in the following words:

All the organic tissues of animals are actually globular cells of exceeding smallness, which appear to be united only by a simple adhesive force; thus all tissues, all animal organs, are actually only a cellular tissue variously modified. This uniformity of finer structure proves that organs actually differ among themselves merely in the nature of the substances contained in the vesicular cells, of which they are entirely composed.

Another French naturalist who seems to have escaped recent notice was J. P. F. Turpin, who published in 1826 a remarkable memoir ("Organographie microscopique elementaire et comparée des vegetaux") with a title so complete that it forms an abstract of the contents:

Observations on the origin and first formation of cellular tissue, on the vesicles composing this tissue, considered as distinct individualities having their own vital center of vegetation and propagation and destined to form by agglomeration the composite individuality of all those plants whose organization is composed of more than one vesicle.

In 1830 the German botanist, Meyen, in his "Phytotomie" wrote: "Plant cells appear either singly so that each one forms a single individual, as in some algae and fungi, or they are united together in greater or smaller masses, to constitute a more highly organized plant. Even in this case each cell forms an independent isolated whole; it nourishes itself, builds itself up, and elaborates raw nutrient materials, which it takes up, into very different substances and structures." He even spoke of such cells as "little plants inside larger ones." Meyen also de-

scribed the circulating movement of cell contents, which had previously been observed by Corti in 1774 and by Treviranus in 1811. In his great three-volume work on "Pflanzenphysiologie" (1837), Meyen described cells as the "essential elementary organs of assimilation and construction."

The English botanist, Robert Brown, in 1831 discovered the fact that nuclei are present very generally in plant cells. He called attention to the fact that nuclei had previously been seen and figured in cells by Meyen, Purkinje, Brogniart, Braur, *et al.*, but they had been regarded as unimportant. Brown recognized nuclei as important organs of the cell, and his work marks a major stage in the development of the cell theory, especially in regard to the origin of new cells.

Cell division had been seen in filamentous algae by Turpin in 1826 and by Dumortier in 1832. Hugo von Mohl described the formation of division walls separating daughter cells in 1835, and four years later (1839) he figured and described the division of spore mother cells in the scale moss, *Anthosceros*, some of his figures (Figs. 21-23) suggesting that he had seen mitosis. Meyen in his "Neues Systems der Pflanzen-physiologie" (1838) said that cell division is everywhere easily and plainly seen in *Confervae*, *Mycelia*, *Chara* and also in terminal buds and root tips of *Phanerogams*.

All this significant work on cells preceded the famous publication just one hundred years ago by Mathias Schleiden, professor of botany at Jena, entitled "Beiträge zur Phytogenesis" (1838). There is no doubt that Schleiden was a distinguished botanist and that he contributed much of importance to an understanding of the genesis of plant *tissues*, but so far from his being the founder of the *cell theory* it can be truly said that his contributions to this great theory were inferior to those of many of his predecessors. It is one of the amazing facts of scientific history that in many biological textbooks Schleiden is called the founder of the cell theory,



as if he had first discovered that all tissues of plants are composed of cells or that the cell is the universal unit of organic function as well as structure. His own particular contribution was in his opinion the discovery of the way in which new cells arise, and yet this has been known for a hundred years to be not only fundamentally wrong but even fantastic. It is still supposed by some biologists that he first set forth the conclusion that the cell leads an independent life. In the beginning of his famous "Contributions" he says:

Each cell leads a double life: an independent one pertaining to its own development alone, and another incidental, in so far as it has become an integral part of a plant. It is, however, apparent that the vital process of the individual cell must form the very first, absolutely indispensable basis of vegetable physiology and comparative physiology.

Yet thirty years earlier Mirbel had expressed this thought, and twelve years before Turpin had stated it with great clarity, while eight years earlier it had been set forth by the famous German botanist, Meyen, in a still clearer and more accurate manner.

So far as the genesis of new cells is concerned, Schleiden's fantastic views that granules (nucleoli) within cells become cytoblasts (nuclei) and that on one side of these a membrane arises like a watch crystal on a watch to form new cells within the old ones—all this could be charitably set down to that liability to error which we call experience, if it were not for the fact that Schleiden is so lacking in charity toward his predecessors, some of whom happened to be right. For example, he says: "Sprengel's pretended primitive cells have long since been shown to be solid granules of amyllum. To enter upon Raspail's work appears to me incompatible with the dignity of science. Mirbel does not make any allusion to the process of cell formation." Of Meyen's work he says: "I still have many doubts, the solution of which I had hoped to have found in his 'Physiology,' but hoped in vain." He either underestimated or ignored the work of Mirbel, Meyen, Turpin and especially von Mohl on cell division. On the whole

one gets a very unpleasant picture of Schleiden's relations to his predecessors and contemporaries, and the question forces itself upon us, "How did he come to be recognized as the founder of the cell theory?" I once heard a distinguished physiologist say that there are two ways to gain recognition, either brag or fight. It seems to me that Schleiden did both. But while he was not the founder nor even an important contributor to the cell theory he did make important contributions to the transformation of embryonic cells into the tissue cells of plants. Nevertheless, it is still a mystery how it has happened that he occupies so high a place in the annals of science; his cell theory had no great significance for botany, since it met with immediate and open opposition by all those who had championed cell division as the method of cell genesis, and especially by Meyen (1839), who stoutly maintained that cells arise by self-division.

Julius von Sachs, in his celebrated "History of Botany," says of Schleiden and his work (p. 188):

Endowed with too great love of combat, and armed with a pen regardless of the wounds it inflicted, ready to strike at any moment, and very prone to exaggeration, Schleiden was just the man needed in the state in which botany then was. His first appearance on the scene was greeted with joy by the most eminent among those who afterwards, contributed to the real advance of the science, though their paths it is true diverged considerably at a later period, when the time of reconstruction was come. If we were to estimate Schleiden's merit only by the facts which he discovered, we should scarcely place him above the level of ordinarily good botanists; we should have to reckon up a list of good monographs, numerous refutations of ancient errors and the like; the most important of the theories which he proposed, and over which vigorous war was waged among botanists during many years, have long since been set aside. His true historical importance has been already intimated; his great merit as a botanist is due not to what he did as an original investigator, but to the impulse he gave to investigation, to the aim and object he set up for himself and others, and opposed in its greatness to the petty character of the text-books. He smoothed the way for those who could and would do great service.

Again, after sketching the earlier work on the cell theory, von Sachs says:

Schleiden's behavior was different. After having somewhat hastily observed the free cell formation (*sic*) in the embryo sac of phanerogams in 1838, he proceeded at once to frame a theory upon it which was to apply

to all cases of cell formation, and especially to that in growing organs. The very positive way in which he announced this theory and set aside every objection which was made to it combined with his great reputation at the time, at once procured for it the consideration of botanists generally. (p. 311.)

Schleiden's theory of cell formation arose out of a curious mixing together of obscure observations and preconceived opinions . . . his theory did not rest on any thorough course of observation. (p. 323.)

We make acquaintance with Schleiden's theory of cell-formation in its original form, if we turn to his treatise, "*Beiträge zur Phytogenesis*" (1838). The work begins with some remarks on the general and fundamental laws of human reason, etc., discusses the literature of cell-formation in a few lines without mentioning von Mohl's numerous observation, goes on to mention the general occurrence of the nucleus . . . then occupies itself with gum, sugar and starch, and at last comes to the main subject. (p. 323.)

Then follows his erroneous description of new cell formation and the contradictions which it aroused by Unger, von Mohl and finally Nägeli.

The first result was that Schleiden found himself obliged to accept the cell-division established by Nägeli in algae and the mother cells of pollen as a *second kind of cell-formation*; thus began the movement in retreat which was destined to end in the following year (1846) with the overthrow of Schleiden's theory. (p. 331.)

Theodore Schwann, the distinguished professor of anatomy at Louvain and Liège, took over the erroneous views of Schleiden as to cell genesis and proceeded to apply them to animal cells. Dutrochet (1824), Purkinje (1837) and Valentin (1838) had observed and described animal cells and compared them with plant cells, but only Dutrochet before Schwann had taught that all the many kinds of animal tissues are everywhere derived from cells as the elementary type of organism. Schwann held that all the different kinds of cells are morphologically related because they all arise by the same process, namely, from granules (nucleoli) which become nuclei and which in turn give rise to the cell body. Unlike Schleiden he held that this genesis could take place in spaces between cells, as well as within mother cells. These erroneous views persisted for a long time under the caption of "free cell formation." Fifty years ago I heard this idea presented in lectures on general biology.

The work of Schwann formed the basis of the theory of the "cell state," which maintained that "cells are organisms and that entire animals and plants are aggregates of these organisms arranged according to definite laws." This theory had a long life and is still probably true in part, but in its extreme form its inadequacies were pointed out by Whitman (1893) and by many experimental embryologists, who have called attention to "the organism as a whole."

The principal contributions of both Schleiden and Schwann were in determining the cellular origins of tissues and not, as they supposed, the origins of new cells. They were not the first to develop this tissue theory, but they were important contributors to it. In view of the fact that all discoveries are based upon previous ones and that science is possible only by such cooperation, I suggest that it would be more accurate as well as more becoming to strike out of our literature these personal possession tags attached to important discoveries, such as the foramen of Monro, the islands of Langerhans, or the cell theory of Schleiden and Schwann.

*(This symposium will be concluded in the January-February issue.)*

# MASS MUTATION IN THE FLORIDA STOCK OF *DROSOPHILA MELANOGASTER*<sup>1</sup>

(Details of an old experiment reinterpreted)

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IN 1929<sup>2</sup> I described a case of what looked like mass mutation after treatment of larvae of Florida stock with heat shocks. Though it has since been confirmed by a number of authors that heat shocks increase the mutation rate beyond the amount of an ordinary temperature function, no similar case of mass mutations has been found. I have myself performed since innumerable heat shock experiments (not published) without finding a similar case, and the same is true for other authors. The majority of geneticists therefore assume tacitly or openly that the original finding was based upon an experimental error, this being the easiest escape from uncomfortable facts. But there was no experimental error, as will be easily seen from an inspection of the details of the experiment. These have not been published thus far, as I was waiting either for a successful repetition or an explanation of the results. This, I think, can now be given: What looked like an effect of the heat treatment was nothing but a chance coincidence of one of the rare cases of spontaneous mass mutation with the heat experiments.

As a matter of fact the correct explanation could have been derived already from certain points in the preliminary description of the facts, which excluded the original explanation. But just as I was blinded by the coincidence with a heat experiment, neither did others who repeated, quoted or criticized the experiment perceive the possibility of spontaneous mass-mutation as the proper explanation. But during the intervening ten years five more cases of mass-mutation, closely paralleling this first one, have been

<sup>1</sup> Assistance rendered by the personnel of Works Progress Administration Official Project No. 465-03-3-192 is acknowledged.

<sup>2</sup> *Biolog. Centralbl.*, 49, 1929.

found and described more or less thoroughly. I myself found two, which, this time, are being analyzed completely, and the very interesting details will be presented in time. (Unfortunately the completion of the work has been since retarded by enforced long interruptions.<sup>3</sup>) One case each was found by Plough and Holthausen<sup>4</sup> and by Demerec,<sup>5</sup> both involving the same Florida stock as my first case. Recently another case, again of the same general type as the others, was found by Valadares<sup>6</sup> and it ought to be added that Spencer<sup>7</sup> had concluded from statistical studies that mutants in *Drosophila* do not appear haphazard, but in clusters. Mass mutation, then, is an apparently rare (?) but absolutely proven phenomenon, which will be of the greatest theoretical importance as soon as we shall know what actually is happening in these cases. Under these circumstances it seems justifiable to publish the details of the first observed case, though a satisfactory analysis was neglected at that time, owing to the wrong interpretation. The material used for this experiment was a long inbred Florida line which did not show any departure from Wild-type in the stocks, in the isolated one-pair bottles which furnished the experimental material or in the controls, derived from the same stock. Unfortunately no controls with brothers and sisters of the experimental flies were run, which would have shown up the situation at once. (Cousins of different grades furnished the controls.) Whatever heterozygosity or contamination could have been present in the material ought, however, to have become visible in time in the actual controls, but for the remote possibility that only the one pair which started the experiment had been contaminated by five different stocks and none of his sisters and brothers who furnished the controls, which were run in huge numbers. We shall see below that one definite finding would have required a con-

<sup>3</sup> See Preliminary Note, *Proc. Nat. Acad. Sci., Washington*, 1937.

<sup>4</sup> *AM. NAT.*, 65, 1937.

<sup>5</sup> *Genetics*, 22, 1937.

<sup>6</sup> *Revista Agronóm.*, 25, 1938.

<sup>7</sup> *AM. NAT.*, 69, 1935.



tamination at least three generations before the experiment started, with an additional, improbable series of favorable events. There is in addition one mutant form which had never existed before in the laboratory (as a matter of fact a new one) and other features to be reported, which exclude absolutely an experimental error. The perfectly parallel features of the results of other authors, just mentioned, add to the safety of this conclusion.

The bottles made up for the heat treatment contained about five pairs of Florida flies, brothers and sisters, all derived from a one-pair mating. There were twelve bottles, containing brothers and sisters, and in addition each group of animals was permitted to lay eggs four times for 24 hours, thus giving 48 bottles, 4 bottles to one group of brothers and sisters each. These were used for the heat exposures of larvae, which kills or sterilizes a majority of individuals, though not in all cases. Therefore only a relatively small number of successful matings could be obtained from the treated flies. This again led to the frequent use of mass matings (see below). The parents of this experiment then were all brothers and sisters, and the flies from heat-treated bottles were all grandchildren of one pair of Florida flies. For the purposes of description the flies from heat-treated larvae may then be called  $F_2$ .

As was described in my paper of 1929 and elaborated in more detail in 1935,<sup>8</sup> the heat-treated flies show in a rather regular manner the phenotypes of many standard mutants in not-heritable form as so-called phenocopies. But in addition to these a small number of individuals occurred in  $F_2$  showing the types which appeared as "mutants" in later generations. These individuals are of special importance. Unfortunately the ratio in which they appeared is not accessible to analysis, because 4 to 5 pairs had to be mated to secure enough offspring after treatment. The lethality of treated larvae in addition might be selective. But we shall see that the ratios in  $F_3$  are not mendelian either, and therefore we may assume that the non-

<sup>8</sup> *Zeitschr. ind. Abstammgl.* 69, 1935.

mendelian ratios in  $F_2$  are also significant. From 20 of the 48  $F_2$ -bottles an  $F_3$  generation could be obtained. Four of these 20 bottles contained flies phenotypically identical with the "mutants" appearing in further generations. The few fertile ones inherited their type, as will be seen. The four  $F_2$  cases are (normal means neither of the latter mutant types; abnormal bristles and inconspicuous eye-colors were not checked in this experiment):

No. II Ab 70 ♀ ♂ normal 4 ♀ 3 ♂ sooty

No. III Be 114 ♀ ♂ normal 1 ♀ sooty, aristapedia, rolled

No. IV Ab 57 ♀ ♂ normal 1 ♂ sooty

No. IV Ac (same parents as before) 26 ♀ ♂ normal 1 ♀ 2 ♂ sooty

Of these "mutant" types only some sooty of the first bottle were fertile. The greatest interest attaches to the one female sooty, aristapedia, rolled, coming from a bottle with a large number of surviving offspring. Let us assume that a contamination had occurred in the Florida stock. Both aristapedia and rolled existed in our stock room, but not in combination. An origin of this individual by contamination would have required: (1) Three independent contaminations in the same bottle by  $e^s$ ,  $ss^a$  (aristapedia) and  $rl$  (rolled) flies; (2) recombination of  $ss^a e^s$  (III) and rolled (II); (3) crossing over between  $ss^a$  and  $e^s$  (only 12 units apart), (4) union of two crossover gametes simultaneously containing the recombination with rolled. As all this would have required at least three generations (and an additional series of pleasant coincidences), it is not to be understood why neither  $P$ ,  $F_1$  or the thousands of flies of the controls ever showed anything. The numerical results of further generations will also exclude the idea of experimental error. It might be added that the bottle in question contained only 30 dead larvae. (These are, of course, the facts which ought to have led to the correct explanation).

From the twenty  $F_2$  broods which contained fertile flies 39  $F_3$  cultures were obtained partly from pair matings, partly from matings of more than one pair. The majority of these  $F_2$  bottles contained a normal number of flies, thus

making a selection of gametes improbable. This fact, by the way, points out that the high degree of sterility in  $F_2$  was at least partly due to genetic causes. Let us first consider the offspring of the  $F_2$  III Bc, which had yielded the sterile aristapedia sooty rolled female, and also the contents of the three other bottles, III B, III Ba, III Bb, which had been stocked with the same parents for 24 hours each. Twelve different  $F_3$  were obtained. From these the following were derived from one pair matings:

(1) Male and female both showing different phenocopic changes of wings, otherwise normal. But it is possible that the female was rolled, as the phenocopy rolled can not be distinguished from the mutant rolled.

$F_3$  (IIIBc<sup>2</sup>d) consisted of:

346	♀	♂	normal
20	♀	♂	sooty
10	♀	♂	rolled
10	♂		white

I add at this point that sooty, rolled, aristapedia, white, have been extracted from this and other broods and turned out to be identical with the standard mutants of that name. (Regarding multiple alleles see below.) The possibility of a position effect at the loci may be excluded by the perfectly normal breeding of the extracted recessives.

In this brood the white might have been produced by a mutation in the mother's ovogonia. But the autosomal recessives, sooty and rolled, could have been produced only in mendelian ratios if a former simple mutation were involved and the parents had been heterozygous.

(2) ♀♂ with changed wings, otherwise normal.

No. III B<sup>2</sup>a 87 ♀♂ 1 ♂ aristapedia

Again not explainable on the basis of a former mutation or contamination.

(3) ♀♂ as before.

No. III Ba<sup>2</sup>d. 24 ♀♂ normal.

The other 9  $F_3$  broods were obtained from 2 to 5 pairs of  $F_2$  flies. As a very large number of treated  $F_2$  flies were

sterile in these experiments, this method of breeding had to be used, as the experiment was meant to discover mutants. Actually of 52 more than one pair-matings 32 produced offspring; of 50 one pair-matings only 7 were fertile. It is to be assumed therefore that among the matings with 2 or more pairs, up to 5, frequently the offspring will actually be the offspring of one pair, though one can never be sure. Five of the 9 successful matings gave only normal offspring. Two of these were bred to  $F_4$ , of which again one bred true to wild type. The other threw in  $F_4$  a few sooty and aristapedia individuals among a multitude of normals (number not recorded but not relevant because more than one pair of parents was used). The other 4 successful  $F_2$  matings were (all parents normal but for phenocopic wing characters):

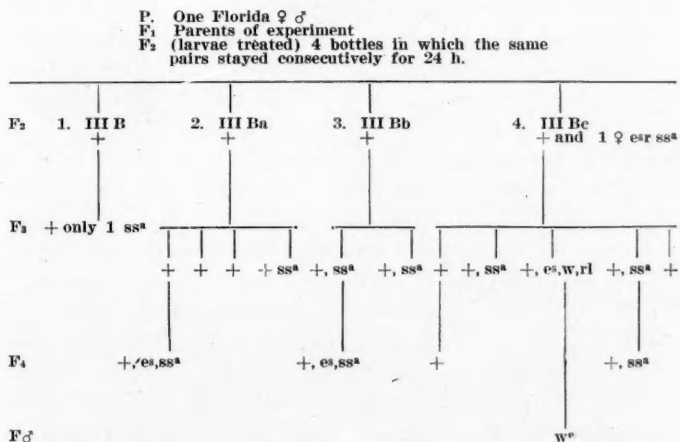
No. III Ba <sup>2</sup> b	24 ♀ ♂ normal	13 ♀ ♂ aristapedia	1 ♀ giant
III Bb <sup>2</sup> b	(2 pairs) 240 ♀ ♂ normal	24 ♀ ♂ aristapedia	
III Bb <sup>2</sup> c	88 ♀ ♂ normal	24 ♀ ♂ aristapedia	
III Be <sup>2</sup> a	116 ♀ ♂ normal	4 ♀ ♂ aristapedia	
III Be <sup>2</sup> g	220 ♀ ♂ normal	11 ♀ ♂ aristapedia	

Many different  $F_4$  were bred from these. Normal flies gave either normals, or normals and aristapedia, or normals, aristapedia, sooty and aristapedia-sooty. Also aristapedia ♀ ♂ threw sooty in  $F_4$ . As most of these broods—with the exception of those in which the mutant types were extracted—were made from more than one normal pair, numbers are not important. But in breeding from single, not mutant, pairs again non-mendelian ratios were observed. Thus the giant ♀ from III Ba<sup>2</sup>b bred to a normal brother yielded hundreds of normal flies and only a few individuals (number not recorded) aristapedia. In  $F_5$  a few giants were recovered and a stock could be established, which later was lost.

We return now to the normal  $F_2$  pair, which in  $F_3$  threw sooty, rolled and white, but no aristapedia, present in many other  $F_3$  of the group. Neither did further generations contain aristapedia, and nothing special happened except for the white locus. The  $F_3$  white ♂ were crossed to normal sisters and recovered according to expectation in half of

the  $F_5$  males. But a few of these were no longer white but eosin. Tested with standard eosin and bred over attached—X they turned out to be real eosin males. When later a homozygous white stock was established it threw besides eosin a few individuals with different eye-colors, which my color vision did not permit me to analyze; however, they appeared to Dr. C. Stern, who worked at that time with me, to be identical with other white alleles. Unfortunately the analysis was not continued, as the work then was going in a different direction. Also the sooty flies produced in these experiments turned out to be of different degrees. By selection, at least three different grades of sooty-ebony were established and bred for some time as different alleles of  $e^s$ . But no further analysis was made.<sup>9</sup> The following pedigree illustrates this first group of facts:

PEDIGREE No. 1



Let us turn now to the second case in which the treated  $F_2$  flies were not all normal. The bottle IIab, derived from

<sup>9</sup> In fact the work was interrupted at that time, as I was leaving for the Far East in the interest of my work on geographic variation. At that time I thought that the experiment might be easily repeated later with similar results, assuming erroneously that the heat shocks were involved. The mutants which appeared were not considered worth keeping as they were obviously identical with the standard ones.

the same grandparents but different parents as the former series, had contained after the heat treatment 70 normal flies, 6 ♀ 1 ♂ sooty. The grandparents had not been sooty; a contamination of the parents with recessive sooty could not have become visible in this generation. The numbers of the following generation will not agree with such an explanation either. (A contamination of the heated bottle itself is excluded by the complex individual discussed before and by the fact that all mutant types have appeared in some  $F_3$  from normal  $F_2$ . A contamination involving mating with the  $F_2$  parents could not produce the  $F_3$  types. In addition the three ebony alleles which were later extracted had never been in our stocks. Only one successful pair mating was obtained, namely, from a sooty pair. This produced 231 ♀ ♂ sooty, 1 ♀ kidney (not sooty!), 1 ♀ aristapedia (11Ab<sup>2</sup>b) (not sooty), 8 ♀ ♂ sooty and kidney. The pair then was homozygous for ebony. But it threw in addition one ♀ each of kidney and aristapedia (not sooty) and 8 kidney ebony combinations. Notice the ratios of the new types which exclude any idea of an error. Here kidney flies were found, missing in the first described line. They were extracted and bred, and as they represented a new type were continued when the other lines were discarded. Only recently two of my former students have analyzed this line (Gottschewsky and Ma, 1937)<sup>10</sup> and they found that it contained two new kidney alleles. (This paper contains the erroneous statement that the mutant is derived from vg-stock. It came from pure Florida stock. The error is based upon an oral communication that kidney appeared later rather frequently in pure vg-stocks.)

Another  $F_3$  was obtained from two pairs, the females sooty, the males normal (II Ab<sup>2</sup>c). The offspring consisted of 303 ♀ ♂ normal, 2 ♀ 1 ♂ aristapedia. Again aristapedia appeared in non-mendelian numbers. Two more broods from more than one normal pair were obtained.

- (1) II Ab<sup>2</sup> ♀ ♂ normal, but a little dusky (probably sooty heterozygous) 285 ♀ ♂, 1 dwarf, some individuals dusky.
- (2) II Ab<sup>2</sup>d 184 ♀ ♂ +, 9 ♀ 5 ♂ light sooty, 1 ♂ light sooty and aristapedia, 1 ♂ dwarf.

<sup>10</sup> *Zeitschr. ind. Abstammgl.* 72.



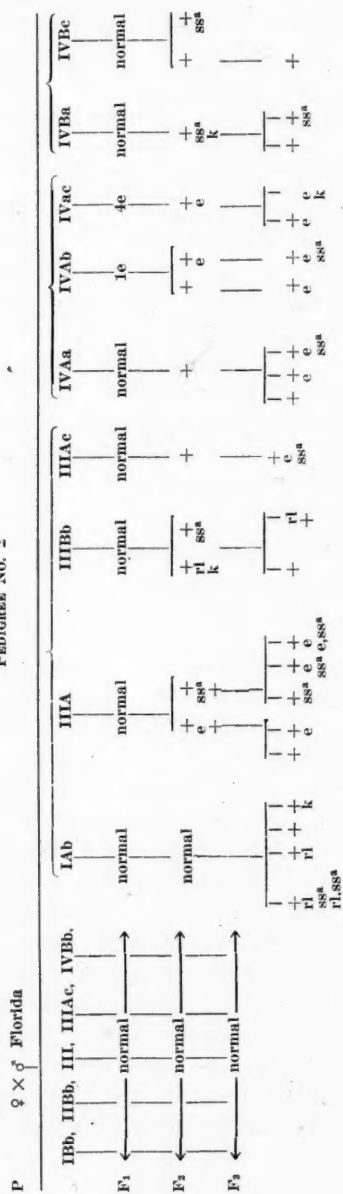
Out of the  $F_4$  derived from these  $F_3$  the following may be recorded:

- (1) from II Ab<sup>2</sup>b (parents one pair sooty)  $F_3$  was all sooty plus a few kidney, aristapedia.
  - II Ab<sup>2</sup>b<sup>2</sup>a ♀ aristapedia × ♂ sooty  
sooty, sooty-kidney and kidney. Only 3 kidney individuals not sooty. Sooty: sooty-kidney = 104: 31.
  - II Ab<sup>2</sup>b<sup>2</sup>c ♀ kidney × ♂ sooty  
118 ♀ ♂ sooty, 16 kidney-sooty, 4 ♀ 6 ♂ kidney, 1 ♀ +
  - II Ab<sup>2</sup>b<sup>2</sup>g ♀ sooty × ♂ sooty-kidney  
52 ♀ ♂ sooty, 24 ♀ ♂ kidney
  - II Ab<sup>2</sup>b<sup>2</sup>b ♀ ♂ sooty, more than one pair  
63 sooty, 7 sooty kidney, 3 aristapedia.
  - II Ab<sup>2</sup>b<sup>2</sup>d dto  
sooty and sooty-kidney
  - II Ab<sup>2</sup>b<sup>2</sup>d dto  
sooty and sooty-kidney
- (2) from II Ab<sup>2</sup>c derived from two pairs sooty × normal  
 $F_3$  was all normal but for a few aristapedia  
 $F_4$  from normal parents contained normals, sooty and aristapedia in one case, only normals in the other.
- (3) from II Ab<sup>2</sup>d, containing only normals, eight sooty and one aristapedia:
  - II Ab<sup>2</sup>dd ♀ light sooty × ♂ no  
all normal or light sooty or sooty (not classified).
  - II Ab<sup>2</sup>dg ♀ ♂ light sooty  
116 ♀ ♂ sooty, 17 ♀ ♂ sooty kidney, again a non-mendelian ratio for the first appearance of kidney.
- (4) from II Ab<sup>2</sup> which contained only normals.
  - 2  $F_4$  all normal
  - 1  $F_4$  135 normals, 9 aristapedia

These data may suffice to show (1) that sooty was homozygous in those  $F_2$  flies which had shown it. (2) that in the offspring of this line again aristapedia and also kidney appeared in a rather erratic fashion, certainly not in mendelian ratios, whenever pair matings were made; (3) that rolled and white were absent in this line derived from brothers-sisters of the foregoing, whereas kidney was absent in the former one.

It is hardly necessary to point out all the details of the other lines, derived from other brothers and sisters in this experiment. I may summarize their parallel results in the following way:

**PEDIGREE No. 2**



(1) Five groups, containing in the treated offspring none of the mutant types, remained normal in  $F_3$  and  $F_4$ .

(2) Three such groups produced only normal offspring in  $F_3$ , but in  $F_4$  two threw sooty and aristapedia and the third aristapedia, rolled and kidney.

(3) All the others behaved essentially like the groups described in detail, namely:

(a) One group threw already a few sooty individuals in  $F_2$ .  $F_3$  from normals contained mostly normals and a few sooty, in  $F_4$  in addition a few aristapedia and kidney appeared.

(b) The others were normal in  $F_2$ . In  $F_3$  one series threw only aristapedia and a single kidney individual among hundreds. The other series (3 bottles from same parents) produced in  $F_3$  sooty, aristapedia, rolled and kidney in significant numbers.

A generalized pedigree (No. 2) of these last groups is found below. The only details which ought to be recorded are the numbers in which the mutant types appeared.

The following table summarizes the important cases:

No.	+	es	ss <sup>a</sup>	k	rl	Gen.	Mating	Pairs P
I Ab <sup>2</sup> b <sup>2</sup> .....	140	..	..	3	..	F <sub>4</sub>	+++	1
I Ab <sup>2</sup> b <sup>2</sup> 2b .....	ca. 200	..	1	..	..	F <sub>5</sub>	+++	more
I Ab <sup>2</sup> b <sup>2</sup> 2a .....	85	5	..	..	..	F <sub>4</sub>	+++	"
III Aa <sup>2</sup> a .....	159	..	3	..	..	F <sub>4</sub>	+++	3 ♀ 1 ♂
III Aa <sup>2</sup> a <sup>2</sup> a .....	79	..	2	..	..	F <sub>5</sub>	+++	more
III Aa <sup>2</sup> a .....	103	1	3	..	..	F <sub>5</sub>	+++	"
III Aa <sup>2</sup> a <sup>2</sup> b .....	72	..	3	..	..	F <sub>5</sub>	+++	"
III Ab <sup>2</sup> b .....	448	..	..	1 k, rl	16	F <sub>4</sub>	+++	"
III Ab <sup>2</sup> b <sup>2</sup> c .....	48	..	..	..	1	F <sub>5</sub>	+++	"
III Ab <sup>2</sup> b <sup>2</sup> b .....	39	..	..	..	3	F <sub>5</sub>	+++	"
IV Ab <sup>2</sup> .....	179	11	..	..	..	F <sub>4</sub>	+++	"
IV Ab <sup>2</sup> .....	116	2	..	..	..	F <sub>5</sub>	+++	2
IV Ab <sup>2</sup> f <sup>2</sup> .....	126	3	9	..	..	F <sub>5</sub>	+++	more
IV Ba <sup>2</sup> b .....	281	..	28	1	..	F <sub>4</sub>	+++	"

Among these there is one pair mating, one mating with one male and one with two pairs. A few individuals, sooty, kidney and aristapedia, appeared. In the other cases, up to four pairs were mated. In three or four instances, one of the mutant types was found in such numbers that a mendelian segregation involving one pair of flies is suspected. In the other cases this is highly improbable. If standing alone the broods from more than one pair would of course not be of any value. Taken together with the identical results of one pair matings, they deserve at least to be recorded. It is needless to say that in all these cases we are dealing with the first appearance of the same mutants in the line. Once present, they breed

according to expectation for ordinary recessive mutants, as was always tested for a few generations.

It is regrettable that at the time when these observations were made their real meaning could not be suspected. Under the impression that a case of heat effect upon mutation, including the so-called parallel induction, was being studied, I was only interested in the appearance of hereditary or not-hereditary types and bred accordingly. Thus the chances for a closer analysis were lost which, however, will soon be finished in another case. Nevertheless the material as it stands seems to parallel the other cases so thoroughly that I feel justified in assuming that here a spontaneous process of mass mutation was actually involved.

#### DISCUSSION

A detailed discussion of this case and an explanation of what has happened will be presented together with the full analysis of the more recent cases. In a general way my opinion is already expressed in the preliminary communication, and all work done since shows it to be correct. This opinion is that mass mutation is the result of very small chromatin-rearrangements (so-called gene mutations), which are caused by already pre-existing chromatin rearrangements probably by favoring "illegitimate" (Darlington, Muller) crossing over. As a matter of fact it could be shown that all stocks, which thus far have produced mass mutation, contained one or more rearrangements. This is true for my two recent cases and for Valadares' case. As it has been shown recently (see Goldschmidt, Gardner and Kodani, *Proc. Nat. Acad. Sci., Washington*, 1939) the standard Florida stock contains a large inversion in the third chromosome. In this stock three of the cases have occurred. We might, therefore, summarize the two other Florida cases shortly.

There is first the case published by Plough and Holt-hausen (1937).<sup>11</sup> They crossed wild-type Florida with black-purple-curved males and backcrossed  $F_1$  with the

<sup>11</sup> AM. NAT., 65, 1937.

latter. Among 300 flies there were 7 showing the mutation blistered wing. Three blistered females were mated to normal brothers, and the offspring was inbred for six generations. In each generation a number of not heritable variants were found as well as sterile types. This is, by the way, also the case in my work, and it is exactly what is expected from chromatin rearrangements. In addition a series of mutants appeared, most of them appearing several times. Among these is an extreme plexus, abnormal abdomen and scute. The authors conclude that the "mutating period" was initiated by a genetic change within a single individual, and they think of a mutability stimulating factor as described by Demerec for the Florida stock (see below). No exact pedigree has been published, but as far as the information goes this case closely parallels the one described here.

In a series of papers<sup>12</sup> Demerec reported upon a gene for mutability in Florida stock. In the presence of both second chromosomes from this stock the rate of lethal mutations at many points of the X-chromosome was very high. In addition after crossing this line a high percentage of visible mutants was produced, among them yellow not less than twenty-four times, and others also repeatedly. The lethals found could not be associated with chromatin rearrangements. Demerec does not seem to take any offence at assuming as explanation a mutated gene which caused one and the same locus in another chromosome, and different ones at that, to mutate constantly. This most wonderful of all "genes" ever discovered was unfortunately lost. Homozygous lethal chromatin rearrangements without visible effect are, if not suspected, easily lost.

<sup>12</sup> *Genetics*, 22, 1937.

## SHORTER ARTICLES AND DISCUSSION

### THE CHROMOSOMAL CREPUSCULUM

THERE is no phase of cytological research which is more involved in confusion both of thought and consequently of terminology than is the reduction in number of the chromosomes, which has long been known in connection with reproduction in both plants and animals. This obscurity is the natural result of difficulties both in matters of technique and in observation. Until comparatively recently little has been known of the internal organization of chromosomes. As a result of improvements in methods of fixation it is now clear, in all cases where observations have been made on material in which the size of the chromosomes is sufficient to permit reliable inferences as to structure, that the organization of somatic and reproductive chromosomes is identical. It has been supposed that at the metaphase of division the somatic chromosomes carry only two interwound spirals or chromatids. In contrast the reproductive meiotic chromosomes contain four chromatids. Observations on the plant side in the case of *Trillium*, *Lilium*, *Gasteria* and *Tradescantia* make it clear that as regards internal organization all chromosomes have the same structure at comparable stages of nuclear division. Doubtless were the chromosomes of animals in general as large as those of plants a similar conclusion would and should be reached.

The greatest confusion has obtained in the case of the all-important stage in which the reduction of number in chromosomes occurs in the passage from the somatic to the reproductive cycle. The older view, which for example is presented in the second edition of Wilson's classic, "*The Cell in Development and Inheritance*," is expressed by the following quotation: "The first indication of numerical reduction appears through the segmentation of the spireme-thread or the resolution of the nuclear reticulum, into a number of masses *one half that of the somatic chromosomes*. In nearly all higher animals this process first takes place two cell-generations before the formation of the definitive germ-cells." Equally categorical statements have been made on the botanical side by Strasburger and others. More recently and notably in the much enlarged third edition of Wilson's classic volume, a very different point of view has been adopted ("*The Cell in Development and Inheritance*," Macmillan



Company, New York, 1928). According to the later view the nuclear filament (spireme) is no longer regarded in general as primitively continuous but constituted by separate chromosomes. In the soma or body these are  $2N$  or  $2X$  in number. In the transition to the reproductive phase somatic chromosomes by the so-called process of synapsis or syndesis become associated in pairs, the supposed synaptic or syndetic mates. In these pairs one element is in general regarded as of female paternal origin and the other of male. Shortly after association, the mates again separate at the anaphase of the first meiotic division. This hypothesis presents a serious logical defect, since it necessarily assumes that the chromosomes of the parent sexes remain permanently distinct, and as a result there can, on a chromosomal basis at any rate, be no crossing over of parental characters such as is quite generally observed genetically in the offspring. It further presents the fundamental difficulty that in reproduction the chromosomes only meet for an obviously futile parting.

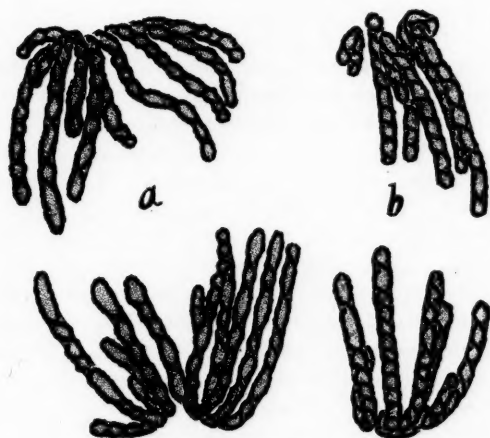
This difficulty has doubtless favored the appearance of the chiasmotype hypothesis of Janssens ("La Cellule," 1909). This theory, criticized by Wilson in his third edition, has been nevertheless adopted by T. H. Morgan and his numerous followers in connection with experimental genetics. In its latest form, the hypothesis assumes that the reproductive chromosomes are not only haploidal in number but also in contrast to the somatic chromosomes in their simplest condition present a single chromatid instead of the two which appear in the diploidal somatic cells. In a manner which remains obscure in the works of these writers the two chromatids of the somatic or sporophytic cells become single as a preliminary to the supposed synaptic pairing. This originally single chromatidal equipment of the reproductive elements is present not only in the first meiotic division but also in the second and is consequently supposed to be characteristic of the gametes or ultimate reproductive elements. As a result of sexual union the chromosomes once more become diploidal in number and also now carry two chromatids, in contrast to the supposed single chromatids of the chromosomes of the reproductive sequence. By some curious logical legerdemain, the somatic chromosomes double in number and carrying two chromatids are supposed to emerge from the resting stage preliminary to meiosis still in the diploid number but now possessed of only single chromatids. In the prophase of the first meiotic division these

single chromatids are imagined to pair and to undergo chiasmatic involvements before separating once more in the second meiotic maturation reproductive division. In the sexual union following meiosis double chromatids are again established in the divisions of the chromosomes of the fertilized egg and the soma of which it is the initial stage.

It is obviously necessary in connection with the involved and too largely hypothetical course of events outlined in the preceding paragraph that the gametes must always possess chromosomes with a single chromatid, and that this assumption must also be made for the two meiotic divisions which lead to their formation. In the case of the higher animals it is quite difficult to arrive at clarity in the situation on account of the relatively small size of the chromosomes and of the close proximity of the appearance of the gametes to the actual meiotic divisions. The higher plants present a very different and much more favorable situation. Here meiosis does not lead directly to the formation of gametes, but these make their appearance in connection with sex-organs or cells formed on a special sexual soma. Thus the confused situation, to which the name *crepusculum* has been applied in the title, is clarified since we have to do with a more or less prolonged series of divisions in cells of the reproductive category. Further, the divisions do not start from an obscure resting phase, extremely difficult to decipher microscopically, but are continuous and consecutive.

Among the higher plants certain of the Monocotyledons have shown themselves as particularly favorable for cytological investigation on account of the large size of their chromosomes. The genus *Trillium* of American and Asiatic distribution has proved to be outstanding in this respect and has been investigated cytologically by a large number of cytologists. They have, however, without exception failed to realize the importance of the gametophytic divisions in connection with any durable hypothesis of the relation of chromosomes to heredity.

It will be useful in the present connection to indicate the organization of the chromosomes in their simplest form as illustrated by the anaphase (the telophase and early prophase present comparable conditions) of nuclear division as exemplified by the soma. Fig. A shows a later anaphase from the root of *Trillium*. Obviously the two groups which foreshadow the formation of daughter cells are characterized by the presence of chromosomes



FIGS. A and B.

in which there are present two reversely coiled chromatids. This situation has been found to exist in a large number of cases, not only in numerous species of *Trillium* but also in *Lilium*, *Erythronium*, *Tradescantia*, *Gasteria*, etc.

In Fig. B is shown the anaphase of the second nuclear division in the sexual soma or gametophyte of *Trillium erectum*. In accordance with the chiasmotype hypothesis of crossing over, the chromosomes of the gametophytic divisions of *Trillium* should contain only a single chromatid. Quite clearly they do not differ in any way from those of the ordinary vegetative soma. We have studied all the divisions involved in the reproductive processes in *Trillium*, including the meiotic as well as the gametophytic ones, and in all instances we have found the chromosomes to present the same organization as the ordinary somatic ones. Similar conditions are found in the male gametophytes, but naturally less clearly as a result of the relative degeneracy of the male sexual generation. Corresponding results have been obtained in the case of genera *Lilium*, *Erythronium*, *Tradescantia* and *Gasteria*.

A detailed comparative examination of the structure of chromosomes in the somatic, meiotic and gametophytic divisions in the present connection have made it clear that their organization as revealed by the microscope is always essentially the same. They contain in every instance two spirally wound chromonemata or chromatids presenting the features of association which in the

case of the meiotic chromosomes has been interpreted as chiasmotypy. If chiasmotypy is present in the chromosomes involved in the reduction division, it is likewise clearly present in all chromosomes, whether reproductive, vegetative somatic or sexual somatic. Since the conditions supposed to be present in meiotic chiasmotypy can not by any stretch of scientific imagination be realized in the divisions of the body cells in animals, or in the sporophyte in plants or in the gametophyte in plants, its significant relation to the meiotic processes and to crossing over is subject to serious doubt. It further requires an organization of reproductive chromosomes fundamentally different from that observed microscopically in other chromosomes, namely, the presence of a single internal chromatid instead of the two chromatids found in all other cases. In the case of the sexual soma or gametophyte of the higher plants it has been shown in the present connection, beyond possible question, that the organization of reproductive chromosomes is precisely the same as in those of the body or soma.

The doctrine of chiasmata, invented to mitigate the logical absurdity of chromosomata meeting at meiosis to part again completely at a later stage, is apparently without adequate foundation, when subjected to the test of a wider critical examination. The relatively new discipline of cyto-genetics presents a luxuriant growth of ephemeral hypotheses, which a ripper and wider knowledge will doubtless prune away. Among the first of these excrescences to be excised is apparently the hypothesis of chiasmotypy, since it is founded on no secure, accurate or extensive basis of cytological facts.

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#### THE COLORATION AND COLOR CHANGES OF THE GULF-WEED SHRIMP, *LATREUTES FUCORUM*<sup>1</sup>

THERE are few faunas more complexly and colorfully adapted to their habitat than is the fauna of the floating sargassum weed of the Gulf Stream. One of the foremost among the crustaceans in this regard is the little shrimp, *Latreutes fucorum*, which has an almost endless variety of tints and color patterns, rivalling

<sup>1</sup> Aided by a grant from the J. F. Porter fund, Harvard University.

in diversity those of the Gulf-weed crab, *Planes minutus*, as described by Crozier (1918). Some of the *Latreutes* are uniformly colored pale yellow, yellowish-green, greenish-brown, brown or red and reproduce almost precisely the diverse colors of the algae to which they cling quite tenaciously. Others are mottled, striped or barred and correspond in pattern to the more irregularly colored bits of weed. Some are black or black with white spots and bars, thus resembling to a remarkable extent the purple-black lifeless tips of the algae, together with the encrusting bryozoans. Another and somewhat common coloring is produced by bright blue patches upon the dorsal and lateral surfaces of the animal. In short, it appears that in such crustaceans as *Latreutes* we have one of the highest points of chromatic evolution found in the group. It becomes interesting to us, therefore, to learn something more about the pigments and pigmentary responses of this highly specialized form.

Four kinds of pigments are found in this animal. They are reflecting white, red, yellow and blue pigments. A similar combination of pigments has been described for the chromatophore complex of *Hippolyte varians*, *Leander* and *Palaemonetes* by various investigators. But unlike the littoral forms just described, *Latreutes* has a great abundance of reflecting white pigment which may vary in hue from a yellowish-white throughout the greater part of the integument of the animal to a clear white in patches on the dorsal and lateral surfaces of some color forms. This production of an excessive amount of reflecting yellowish-white pigment can perhaps later be explained in terms of the action of the intense illumination to which these creatures are subjected while floating in weed at the surface of the ocean under a bright subtropical sun, because the other two common shrimp of this habitat, *Leander tenuicornis* and *Hippolyte acuminata*, have likewise a very large amount of this pigment. Thus, these animals are all semi-opaque in contrast to the more familiar transparent shrimp.

The relative abundance of the red, yellow and blue pigments, on the other hand, is subject to much more individual variation. From a single small floating mass of weed it was possible to find an animal of any shade ranging from a pale yellow to black. The former would contain almost no blue and red pigments, while the latter would possess a great deal of these.

Fundamentally, the migrational responses of the pigments within the chromatophores of *Latreutes* was similar to that de-

scribed for *Palaemonetes* by Perkins (1928) and Brown (1935). The red and yellow pigments responded to a white background by concentration into the chromatophore centers, and to a black background by dispersion into the chromatophore branches. Darkness produced a concentration of these pigments, as did also an injection of sea-water extract of the eyestalks of *Leander affinis*.

A variation in the pigmentary behavior was seen, however, in the responses of the reflecting white chromatophores in animals kept upon a black background. Darkness or a black background with low intensity of incident light, such as is found in an ordinary laboratory, would call forth a concentration of this pigment. The direct light of a bright sky or sunlight would produce a dispersion of this pigment in spite of the black background. It will require more experiments to determine whether this is an instance of the direct effect of light upon the chromatophore as believed by Stephenson (1934) to hold true for *Leander*, or whether the eye is involved here as it is in background adaptation. At all events, if the theory of Keeble and Gamble (1904) that a dispersed pigment increases in amount and a concentrated one decreases is true, we have a part explanation of the abundance of this reflecting yellowish-white pigment within these animals accustomed to the intense light found in the ocean surface.

An examination of the blue patches which occurred in many of the animals showed them to consist of chromatophores which were apparently filled with a blue pigment and which physiologically behaved as the reflecting white. When a piece of the integument containing a few of these blue chromatophores was treated with 70 per cent. alcohol while being viewed microscopically by reflected light, it was seen that as the alcohol reached the chromatophore the blue pigment was first transformed into red and then dissolved out, leaving a clear white chromatophore which resembled the normal white ones in appearance. This observation, together with the physiological responses of these blue chromatophores, strongly suggest that here it is merely a case of accumulation of the blue pigment within particular white chromatophores and thus masking them.

In view of the recent advances in the knowledge of the physiology of color change in decapod crustaceans it is improbable that the different color patterns are solely the results of the responses of the animals to individual situations, though this may hold true to some extent. Examination of many animals seems to indicate



that here we are dealing with a specific and inborn basic pattern which in an individual animal is repressed or encouraged by light intensity and color of the background. For instance, when clear white patches are present upon the animal they are restricted to particular regions of the body. Comparable white areas quite constant in position were also described by Crozier to be present in *Planes minutus*.

The shrimps vary in the degree to which these white regions are encroached upon or replaced by the colored pigments, a cardiac bar being the one most persistently present. A reddish brown animal having a very prominent white cardiac bar was placed in a black dish in a dimly lighted room. The white pigment of the bar concentrated into chromatophore centers and remained so during the major part of a five-day interval. At the end of this time the animal was subjected again to bright illumination to produce dispersion of the white pigment, but now the area was tinted by red and blue pigments which had formed in this region during the experimental period. And too, the area covered by the whitish patch seemed to have decreased.

Similarly, the blue spots which are upon some animals are probably subject to the same explanation. When found in animals they are more or less constant in magnitude and position.

What is perhaps most interesting in this report is a description of the wide variety of colors and color patterns in an animal which conforms in most simple responses to crustaceans having far less color change ability. *Latreutes* rivals or surpasses in its color varieties *Hippolyte varians* investigated early in this century by Gamble and Keeble (1900). Some aspects of the color changes in this latter species have been recently reinvestigated by Kleinholz and Welsh (1937). Both *Latreutes* and *Hippolyte* should be re-examined in detail in the light of our present knowledge of hormonal control of the chromatophore complex.

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#### A NEW ALLELE IN THE WHITE SERIES OF DROSOPHILA AND ITS RELATIONSHIP TO SOME OTHER WHITE ALLELES

THERE are many series of multiple alleles which can be arranged according to phenotype in a simple quantitative series. Their compounds with each other also fit into a sequence in which the same order is observed.

This typical behavior is often ascribed to the familiar alleles of white in *Drosophila melanogaster* of which at least fourteen are now known. Dunn (1935) gives a summary of their colors and interrelations. A new member of this series, pearl ( $w^p$ ), has been reported recently by Steinberg (1937). The mutant appeared on February 17, 1937, as a single male in a stock *fj px sp* (Columbia stock 36) and was extracted from a cross of the original male by Oregon wild type. The new mutant has now been studied in compound with several other alleles of white, and a departure observed from the usual rule that the alleles at this locus fall into the same serial order of effect in both homozygotes and compounds.

Seven alleles of white (eosin  $w^e$ , cherry  $w^{ch}$ , apricot  $w^a$ , honey  $w^h$ , tinged  $w^t$ , pearl  $w^p$ , and white  $w$ ) were employed in this experiment. They are arranged below in order of decreasing darkness:<sup>1</sup>

$$w^e \text{ } \varnothing > w^{ch} \text{ } \varnothing > w^a \text{ } \delta \cong w^{ch} \text{ } \delta \cong w^e \text{ } \delta > w^a \text{ } \varnothing >> \\ w^h \text{ } \varnothing > w^h \text{ } \delta >> w^t \text{ } \delta = w^t \text{ } \varnothing > w^p \text{ } \delta = w^p \text{ } \varnothing > w \text{ } \delta = w \text{ } \varnothing$$

The above sequence follows previous results closely with the exception of  $w^{ch} \text{ } \delta >> w^a \text{ } \delta$  as reported by Dunn. It has been found that  $w^a \text{ } \delta \cong w^{ch} \text{ } \delta$  is probably the condition in the stocks used in the present experiments.

The qualitative contributions made by the alleles white, pearl and tinged have been carefully studied since their color intensities

<sup>1</sup> Definitions of symbols used: = approximately of same intensity, neither sharply nor consistently darker or lighter than; > definitely and regularly darker than; >> regularly very much darker than;  $\cong$  definitely darker than in at least 75 per cent. of the comparisons, the rest being borderline cases.

are very similar. However, they may be separated from each other *easily* and *quantitatively*. Thus white and pearl can be told apart with the naked eye. The eye color of the white mutant approximates the flat white of milk, while pearl is aptly described by the light yellow of cream or butter. Age offers no obstacle to separation, for the eyes of pearl flies not over ten minutes old are unmistakably darker than the eyes of white flies which have been aged for a few days. Unlike white, pearl eyes do change slowly with age when their early dull ashen-yellow cast deepens slightly.

The separation of pearl from tinged is not as clear as that of pearl from white, because the color difference between pearl and tinged is more one of quality than of brightness or darkness. Actually pearl appears slightly "darker" or duller than tinged, but tinged is placed closer to the dark end of the series since it shows more of the "red" ingredient. One can see traces of pink in tinged that are never recognized in pearl or in white. Here it should be recalled that the wild-type eye contains yellow, orange and red pigment granules and that the red granules represent the highest state of reduction (Schultz, 1935). It is therefore probable that the presence of pink in tinged indicates the attainment of a higher threshold or state of reduction than the yellow threshold of pearl, but this is not definitely known. The apparent color disparity might just as well be caused by a differential distribution of variously colored pigment granules in tinged and in pearl. However, the threshold distinction is important for the possible bearing it has on the contribution of the two alleles to compounds of each with some third darker allele.

In white, pearl and tinged mutants, males and females have practically identical eye-color intensities. This only shows, qualitatively at least, that the eye color remains constant whether one or two of these sex-linked alleles may be present. However, one has the advantage of knowing from this that in the production of a compound of one of these alleles with some fourth darker allele, the addition of the gene of the darker allele, rather than the addition of the X chromosome in which it rests, will probably be the more material factor in influencing the phenotype of that compound.

Having established the color differences among the pure types, and having clearly shown the relation of pearl to white and tinged, compounds were made up in which the effects of honey, tinged, pearl and white could be compared in compound with the

darker alleles, eosin, cherry and apricot. These were obtained by crossing stocks containing the desired alleles; the stocks used were not known to be otherwise isogenic. When hatching began, the culture bottles were cleared approximately every hour, so that the eye colors of the female compounds could be compared at early and known ages. A comparison of older females of known age was made by aging the newly hatched females in separate vials. The eyes were examined in blue-green light reflected from a white porcelain plate. An effort was made to eliminate shadows, bright areas and chromatic aberration. Frequently the positions of the flies on the porcelain were interchanged to determine whether the observed differences were actual or due merely to variations in intensity of illumination of the field.

The results may be summarized by arranging the compounds in order of decreasing darkness from left to right.

Apricot compounds:

average age 1.5 hours  $w^h/w^a >> w^t/w^a > w/w^a = w^v/w^a$   
 average age 5 hours  $w^h/w^a >> w^t/w^a > w/w^a \cong w^v/w^a$

Cherry compounds:

average age 1 hour  $w^h/w^{ch} >> w^t/w^{ch} > w/w^{ch} \cong w^v/w^{ch}$   
 average age 8 hours  $w^h/w^{ch} > w^t/w^{ch} \cong w/w^{ch} > w^v/w^{ch}$

Eosin compounds:

average age 2.5 hours  $w^h/w^e >> w^t/w^e \cong w/w^e > w^v/w^e$   
 average age 5 hours  $w^h/w^e > w^t/w^e = w/w^e >> w^v/w^e$

The results indicate an unexpected reversal of order wherein the pearl compounds are lighter than corresponding white compounds, although pearl homozygotes are darker than white. The rest of the seriation agrees with what one might anticipate. The reversal was so unusual that the experiment was repeated more carefully. In the repetition, honey compounds with eosin, cherry and apricot were omitted, since there was no doubt about their relation to the corresponding compounds of tinged. Honey was now used as a fourth allele with which white, pearl and tinged could be compounded. Care was taken to regulate humidity, temperature (range of 22 to 27° C.), and to standardize the food.

The results of the second experiment are outlined below:

Honey compounds:	age not over 1.5 hours	$w^t/w^h >> w/w^h = w^v/w^h$
	number of flies compared	20      38      39
	average age 5 days	$w^t/w^h > w/w^h = w^v/w^h$
	number of flies compared	6      29      26
Apricot compounds:	age not over 1.5 hours	$w^t/w^a > w/w^a = w^v/w^a$
	number of flies compared	10      35      30
	average age 5 days	$w^t/w^a > w/w^a = w^v/w^a$
	number of flies compared	8      28      27

Cherry compounds:	age not over 2 hours	$w^t/w^{ch} \geq w/w^{ch} > w^p/w^{ch}$
	number of flies compared	14      10      10
	age not over 3 hours	$w^t/w^{ch} = w/w^{ch} > w^p/w^{ch}$
	number of flies compared	19      19      15
Eosin compounds:	average age 5 days	$w^t/w^{ch} \geq w/w^{ch} > w^p/w^{ch}$
	number of flies compared	21      13      16
	age not over 2 hours	$w^t/w^e = w/w^e > w^p/w^e$
	number of flies compared	14      19      31
	average age 5 days	$w^t/w^e = w/w^e > w^p/w^e$
	number of flies compared	11      18      29

Except for a few minor inconsistencies the two sets of data show good agreement. For instance, the initial work gave  $w/w^a \geq w^p/w^a$ , which is not confirmed by the second observation  $w/w^a = w^p/w^a$ . To be sure, there were among the latter some  $w/w^a > w^p/w^a$ , but there were also a few  $w^p/w^a > w/w^a$ , with the greatest number being inseparable. Faced with results neither consistent nor sharp the safest decision seemed to be  $w/w^a = w^p/w^a$ . This inconsistency was also noted in the new honey compounds, which fitted into a series similar to that of the apricot compounds.

About 25 to 50 per cent. of the three-hour-old cherry and five-day-old eosin compounds included such relationships as  $w/w^{ch} > w^t/w^{ch}$  and  $w/w^e > w^t/w^e$ , respectively. But the inverse order also existed in these cases and warranted the insertion of an equality sign. The reason why the white compounds often equal or surpass the color intensity of the tinged compounds of cherry and eosin is probably that, given enough time (five days), the former finally catch up with the latter; that is, the rate of pigment reduction is slower in the white than in the tinged compounds, but the white compounds ultimately reach a state of heavy pigmentation.

The best agreement of data was achieved among the eosin and cherry compounds, as the following comparisons show:

Cherry compounds:	First run, age about 2 hours	$w^t/w^{ch} \geq w/w^{ch} \geq w^p/w^{ch}$
	Second run, age about 2 hours	$w^t/w^{ch} \geq w/w^{ch} > w^p/w^{ch}$
	First run, age about 8 hours	$w^t/w^{ch} \geq w/w^{ch} > w^p/w^{ch}$
	Second run, age about 5 days	$w^t/w^{ch} \geq w/w^{ch} > w^p/w^{ch}$
Eosin compounds:	First run, age about 2 hours	$w^t/w^e \geq w/w^e > w^p/w^e$
	Second run, age about 2 hours	$w^t/w^e = w/w^e > w^p/w^e$
	First run, age about 5 hours	$w^t/w^e = w/w^e > w^p/w^e$
	Second run, age about 5 days	$w^t/w^e = w/w^e > w^p/w^e$

In compound with these two darker alleles, the diluting effect of pearl was always greater than that of white.

A few observations were made of pearl when placed opposite a deficiency, Notch 8. At ages from three hours to five days  $w^p w^p$  was always definitely darker than  $w^p/N8$ . This shows that pearl behaves like other white alleles when opposite a deficiency.

## DISCUSSION AND SUMMARY

The seriation found above in the white and tinged compounds of honey, apricot, cherry and eosin may be regarded as agreeing with the essentials of the usual rate concept. Proceeding from wild type to white, the sequence could be described by assigning to each allele a decreasing rate of reduction on some basic pigment substance. Assuming that two alleles act independently in a compound and that they are the sole variables involved, then the eye color intensity in the compound should be intermediate between what it is in the two homozygotes. If this is true, then several compounds of a single allele, like eosin, with a few other alleles, like tinged and pearl and white, should fit into a regular series corresponding to the order of darkness of these latter alleles. This is apparently what happens when white and tinged are part of the compound, but not when pearl is involved. The pearl and white compounds show an unexpected reversal.

Not all of the four series of compounds show the same degree of reversal. It occurs quite frequently in cherry and eosin compounds and is very marked in the latter. The same can not be said for honey and apricot compounds, although the evidence does permit the negative conclusion that the pearl compounds of these alleles are not (as one might expect them to be) darker than the white. A generalization can be made in which it appears that the darker the original allele used ( $w^e/w^e > w^{ch}/w^{ch} > w^a/w^a > w^h/w^h$ ), the more striking is the white-pearl reversal, thus at about two hours old,  $w/w^e > w^p/w^e$ ,  $w/w^{ch} \geq w^p/w^{ch}$ ,  $w/w^a = w^p/w^a$ ,  $w/w^h = w^p/w^h$ . An interpretation of this unusual reversal of the order of effects of alleles remains to be found.

The experiments were performed as a member of a course in genetics given by L. C. Dunn and A. G. Steinberg. The observations have since been confirmed by Miss Y. Nakayama.

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